The Acute Effects of Modafinil on Behavioural and ERP Measures of Attention

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Statement

I declare that this thesis is my own work and that, to the best of my knowledge and belief, it does not contain material from published sources without proper acknowledgement.

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Abstract

Modafinil is a wakefulness-promoting drug increasingly used off-label for cognitive neuroenhancement in healthy persons, despite conflicting empirical support. The present study aimed to investigate the effects of 200mg of modafinil on behavioural (reaction time and accuracy) and neural (N1 ERP component) measures of attentional alerting and orienting in healthy humans using a Revised Attentional Network Task paradigm. Healthy non-sleep deprived males (N=18) completed the task at baseline and 3 hours post-ingestion (single dose 200mg modafinil or placebo) in this randomised, double-blind, counterbalanced, within-subjects study. They self-reported mood (Profile of Mood States – Short Form), fatigue (Karolinska Sleepiness Scale) and Subjective Performance and Drug Effects (Visual Analogue Scales). The results indicated that modafinil prevented feelings of fatigue experienced in the placebo condition, enhancing both tonic and phasic alerting attention, as indicated by increased N1 amplitude and reduced RT for no cue and central cue trials. Some enhancement of the orienting network (RT and N1 to spatial cues) was observed, but it was of no greater in magnitude than the alerting effects. Therefore, the orienting effect was likely a consequence of the interdependent nature of the networks. These results are a preliminary indication of the positive effect of modafinil on alerting components of attention in healthy persons. Future research should aim to further substantiate these findings, as the current study was slightly underpowered. Studies should also investigate tentative evidence discovered for enhancement of the executive attentional network, indicated by improved inhibition of incongruent flankers.

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a wakefulness promoting agent (eugeroic) that is increasingly used among healthy people for cognitive neuroenhancement despite unclear empirical support. Modafinil increases dopamine, norepinephrine and orexin levels within the cerebral cortex (Minzenberg & Carter, 2008). As these neurotransmitters are strongly related to each of the alerting, orienting and executive attentional networks, effects of modafinil on these systems are expected (Petersen & Posner, 2012). The neurochemical processes are also responsible for the decreased drowsiness in sleep-deprived individuals (Minzenberg & Carter, 2008). Consequentially, modafinil is listed as a Schedule IV prescription drug to treat somnolence experienced by narcolepsy patients, shift workers and sleep-apnoea sufferers. Amongst these sleep-deprived individuals, Modafinil has been demonstrated to improve cognitive functions (including attention) with similar efficacy to amphetamine drugs, and with reduced occurrence of side effects and addiction (Minzenberg & Carter, 2008). Recent meta-analyses of studies in healthy non sleep-deprived samples report conflicting findings as to whether these neuro-enhancing effects are observed (Battleday & Brem, 2015; Repantis, Schlattmann, Laisney, & Heuser, 2010). Despite this inconclusive evidence, off-label use of modafinil continues in a range of healthy persons including business people, pilots and students (Repantis et al., 2010). It is important to investigate whether modafinil can be neuro-enhancing for healthy non-sleep deprived persons, as use in this population has monetary, legal and moral consequences.

Neurochemical Effects of Modafinil

Modafinil is a psychostimulant that targets the brains sleep and arousal systems. Modafinil causes an increase in catecholamines by directly inhibiting the

uptake transporters for dopamine and noradrenaline (Qu, Huang, Xu, Matsumoto, & Urade, 2008). This results in the rise of cerebral serotonin, orexin and histamine, as well as a concurrent decrease of GABA (Qu et al., 2008). Modafinil's influence on catecholamines and their interaction with the orexins axis likely underlies its promotion of arousal, wakefulness and potentially, attention (Minzenberg & Carter, 2008).

The Attentional Networks

Attention is the function of distributing cognitive resources to stimuli in the environment (Coull, 1998). Petersen and Posner (2012) identified the alerting, orienting and executive systems as three distinct, yet interactive, networks of attention. The role of the alerting network is to prepare the brain to be vigilant in identifying and responding to stimuli. This requires arousal, which relies on norepinephrine. Given that modafinil stimulates norepinephrine production in both the hypothalamus and the prefrontal cortex, it would be expected to enhance performance on alerting tasks (de Saint Hilaire, Orosco, Rouch, Blanc, & Nicolaidis, 2001).

To study alerting, researchers can present participants with a warning cue prior to a target. This elicits phasic alertness, the component of alerting that is responsible for modulating preparedness (Petersen & Posner, 2012). The participant accumulates a heightened sense of expectation for the onset of the target and therefore, responds faster. Alternatively, researchers can investigate tonic alertness, which refers to resting-state arousal (Petersen & Posner, 2012). Tonic alertness can be measured using tasks that measure sustained attention, the ability to maintain vigilance over a prolonged period.

The orienting network is responsible for deploying and shifting attention towards stimuli within the sensory field (Petersen & Posner, 2012). Attention shifting (Vossel, Geng, & Fink, 2014). When important and unexpected stimuli appear in the sensory field, the temporoparietal junction influences the ventral frontal cortex to re-orient attention towards it (Vossel et al., 2014). For example, the ventral system is enacted when a target appears in an unexpected spatial location, such as after an invalid cue. The dorsal orienting system, in contrast, is responsible for the deployment of attention based on expectations (Vossel et al., 2014). This system has two key nodes; the intraparietal sulcus and the frontal eye fields. These areas include retinotopic organisation of maps for the spatial environment which provide a top-down influence on the orienting of attention (Silver & Kastner, 2009). The dorsal network activates to orient attention spatially, such as after a cue that informs the viewer of where an upcoming target will appear in the sensory field.

The executive network of attention facilitates selective attention and the suppression of distractors (Petersen & Posner, 2012). These functions are top-down, rely on the dopamine neurotransmitter, and stem from the anterior cingulate cortex (ACC) and prefrontal brain areas (Posner & Petersen, 1990; Posner, Rueda, & Kanske, 2007). As a single dose of modafinil increases cortical dopamine and activity in the ACC node of the LFPCN, it may enhance executive attention (Esposito et al., 2013).

The Acute Effects of Modafinil on Attention

Studies investigating the attentional effects of modafinil have conflicting findings. Repantis et al. (2010) found that healthy non sleep-deprived individuals had a moderate, significant improvement in their performance on attentional tasks after a single dose of modafinil compared with baseline (d>0.50). The tasks assessed

components of attention that rely on the alerting network (Detection of Repeated Numbers [DRN], Serial Reaction Time [SRT], Rapid Visual Information Processing [RVIP], Mackworth Clock (MC) and other simple RT tasks). Executive attention was not analysed as relevant studies rarely collected baseline data. There was also a lack of research for orienting attention.

Battleday and Brem (2015) conducted a more recent review of the literature, separating studies based on attention type. They observed conflicting results and concluded that the majority had found no enhancement of 'alertness' or 'sustained attention' following administration of modafinil. The inconsistency in findings may be attributed to methodological differences, wherein those studies reporting null effects generally lacked sufficient sensitivity to detect the effects of modafinil. They were potentially underpowered due to ceiling effects, with many of the tasks lacking the cognitive demand for participants to demonstrate improvement. Past studies were also often limited by small samples and failure to adequately address confounding variables (such as IQ, caffeine and nicotine usage).

Modafinil and the Alerting Network

As tonic and phasic alertness share a reliance on norepinephrine, enhancement of either is potential evidence of enhancement for the other. However, the studies that have investigated the effects of modafinil on alertness in healthy samples have had mixed findings (see Table 1). This is likely due to methodological issues, particularly ceiling effects. Only one study investigating the attentional effects of modafinil in a healthy, non sleep deprived sample has included a task designed to elicit both phasic and tonic alertness (Liepert, Allstadt-Schmitz, & Weiller, 2004). These researchers used a reaction time (RT) task with trials that included either no warning signal (measuring tonic alertness) or an alerting cue (an

auditory beep, measuring phasic alertness) that was indicative of an upcoming target (an unspecified go-signal). For all trials, the participants pressed a right-button at target onset. Participants completed this task after receiving placebo or modafinil (Liepert et al., 2004). As expected, RT to the target was significantly faster for trials with a warning cue compared to those with no cue. There was no difference in RT between the modafinil and placebo groups for trials preceded by no cue (g=0.14) or a warning cue (g=0.08) (Liepert et al., 2004). They concluded that modafinil does not enhance tonic or phasic alertness. However, this finding may have been due to a lack of power, as ten participants was unlikely to be sufficient to detect the effect of modafinil in a healthy sample on such a simple task (Liepert et al., 2004). A task with higher cognitive load might allow any improvement to be more observable.

Baranski, Pigeau, Dinich, and Jacobs (2004) used a more difficult task to assess the influence of modafinil on the alerting network. They compared the effects of placebo with modafinil in participants who completed a cognitive battery three times per session (baseline, 90-minutes and 180-minutes post-ingestion). The cognitive battery included the DRN to measure sustained attention; participants viewed changing three-digit numbers on a screen and responded to rare repeated numbers, using a button press. Participants also completed a 3-minute SRT task to measure tonic alertness. When a probe letter appeared at the top of the screen the participant had to move a cursor and click on its matching counterpart amongst flankers at the bottom of the screen. Participants were significantly more accurate on the DRN for modafinil compared with placebo at both post-ingestion testing points. They were also significantly faster on the SRT at 3 hours post-ingestion for the modafinil condition compared with placebo. Furthermore, they reported significantly lower fatigue for the modafinil condition (Baranksi et al., 2004). These findings are

indicative of modafinil enhancing the alerting network. Participants were asked to abstain from caffeine and nicotine for 48 hours before the study. These substances are known to enhance attention and those dependent on them may merely be restored to baseline after ingesting modafinil, rather than experiencing any further enhancement. However, the within-subjects design likely prevented this skewing the results (Baranksi et al., 2004).

Theunissen et al. (2009) compared the cognitive effects of modafinil with other stimulants and placebo. Participants completed the MC task, which measures sustained attention, as part of a larger cognitive battery. This task involved the presentation of 60 grey dots in a circular formation on a screen. The dots illuminated sequentially and the participant was asked to press a button when a dot was skipped. As the skips occured rarely, fewer missed targets and faster RT indicated greater sustained attention. Participants were significantly faster in the modafinil condition relative to placebo (g=2.65), with no significant change in accuracy (Theunissen et al., 2009). This indicates that modafinil enhances alertness. The researchers acknowledged that this finding may generalise poorly as data was missing for three participants, due to computer error.

Table 1

Alerting Effects of Modafinil in Healthy Non-Sleep Deprived Participants

Author	SS	Design	Dose	Measures	Significance (*p*) and Effect Size (*d* or *g*)
Liepert and Weiller (2004)	10M	PC, DB; R; WS	200mg	Alertness (Tonic, Phasic) Simple RT task	No significant difference if performance for modafinil compared with placebo for NC trials (g=0.14) or WC trials (g=0.08). No p value provided.
Baranski et al. (2004)	18M	PC; DB; R; WS	4mg/kg	Sustained attention; DRN	Significantly improved accuracy on DRN for modafinil compared with placebo at both post-ingestion testing points (1.5 hours p<0.003, 3 hours p<0.05).
				Tonic Alertness; SRT	Significantly faster RT on the 3 hour post-ingestion SRT for the modafinil condition compared with placebo. Effect sizes not calculated as standard error/deviation was not provided.

Table 1. Continued.

Alerting Effects of Modafinil in Healthy Non-Sleep Deprived Participants

Authors	SS	Design	Dose	Measures	Significance (*p*) and Effect Size (*d* or *g*)
Theunissen, Elvira Jde, van den Bergh, and Ramaekers (2009)	16 (5M)	PC; DB; R; WS	200mg	Sustained attention: Mackworth Clock Task	Large and significant reduction of RT for MC task for modafinil compared with placebo (p=0.001, g=2.65). No significant change in accuracy (p=N/S).
Randall, Shneerson, and File (2005)	89 (47M, 42F)	PC; DB; R; BS	100/ 200mg	Sustained attention: RVIP; a) RT b) missed targets	Participants were faster in the 200mg modafinil condition compared with placebo, regardless of IQ. However, the magnitude of this effect was much greater for the low IQ group (g=0.43) compared with the high IQ group (g=2.51, d=2.54). Furthermore, the number of missed targets was lower in the modafinil condition across IQ groups, p<0.05, without notable changes in accuracy.

Table 1. Continued.

Alerting Effects of Modafinil in Healthy Non-Sleep Deprived Participants

Authors	SS	Design	Dose	Measures	Significance (*p*) and Effect Size (*d* or *g*)
Turner et al. (2003)	60M	PC; DB; R; BS	100/ 200mg	Sustained attention: RVIP (RT)	No significant difference between the three drug conditions, p=0.915. All effect sizes for differences were less than small (g<0.15)
Winder-Rhodes et al. (2010)	12M	PC; DB; R; WS	300mg	Sustained attention: RVIP a) accuracy b) response bias	a) No significant difference in accuracy between groups, p=0.981, g=0.01 b) No significant difference in response bias between groups, p=0.317, g=0.00

Note: All measures were conducted as a part of larger cognitive batteries. Design abbreviations: M=male; F=female; PC=placebo-controlled; DB=double-blind; R=randomised; WS=within-subjects; BS=between-subjects. Task abbreviations: DRN=Detection of Repeated Numbers; SRT=Serial Reaction Time; RVIP=Rapid Visual Information Processing [RVIP]. Effect sizes not calculated/reported if data absent.

Randall, Shneerson, and File (2005) investigated the effects of modafinil compared with placebo in healthy university students who completed a cognitive battery, including the RVIP, 2-3 hours post-ingestion. The RVIP requires participants to view serially presented digits on a screen and respond with a button press when they detect an infrequent 3-digit sequence. Faster RT and fewer missed targets indicate greater sustained attention. The participants were split according to whether they had lower (≤110) or higher (≥111) IQ (measured with the National Adult Reading Test-II; Nelson and Willison, 1991). Participants were faster in a 200mg modafinil condition compared with placebo. The magnitude of this effect was greater for the low (g=0.43) compared with high IQ group (g=2.51). This study indicates that alertness is enhanced by modafinil, but that this effect may be less observable in simple tasks, particularly if participants have higher IQs.

Turner et al. (2003) and Winder-Rhodes et al. (2010) also used the RVIP to observe the effects of modafinil in healthy samples. Turner et al. (2003) observed non-significant, negligible differences between modafinil and placebo on RVIP performance (all gs<0.15). Similarly, Winder-Rhodes et al. (2010) found no difference in RVIP performance across drug conditions. The mean IQ for both samples was high, and the RVIP was a simple task, which together may have masked any cognitive enhancing effects of modafinil for both studies. Furthermore, Winder-Rhodes et al.'s (2010) participants abstained from caffeine and nicotine pre-session. Any who were dependent users would likely have experienced withdrawal effects, with the modafinil merely returning them back to their baseline cognitive performance.

The Effects of Modafinil on the Orienting Network

Within both sleep deprived and healthy populations there is a lack of research investigating whether modafinil influences orienting attention. Esposito et al. (2013) used fMRI to observe the effects of modafinil (100mg) on resting-state brain activity at baseline and three hours post-ingestion in 26 males. For the modafinil condition, there was a significant increase in activation for both the Dorsal Attention Network (DAN) and the ACC node of the left Frontal Parietal Control Network (LFPCN). The increase in DAN activity indicates that modafinil may enhance performance on orienting tasks by influencing top-down deployment of attention (Esposito et al., 2013). Furthermore, the orienting network can be influenced by the alerting network. For example, if a participant is primed with an alerting cue such as an auditory beep, their RT to a subsequent orienting cue is reduced (Callejas, Lupianez, Funes, & Tudela, 2005). Therefore, it may be expected to improve orienting as a consequence (Baranski et al., 2004; Theunissen et al., 2009, Randall et al., 2005). Alternatively, modafinil might be expected to enhance orienting attention due to its effects on the executive network.

The Effects of Modafinil on the Executive Network

Focusing on a particular aspect of a stimuli (selective attention) and inhibiting irrelevant stimuli (inhibition) are core functions of the executive network of attention that rely on dopamine. Given the capacity of modafinil to increase dopamine production, enhancing effects on tasks involving the executive system are expected. As with the alerting network, some studies have reported null effects, which can again be attributed to methodological issues. For example, studies investigating the effects of modafinil on executive attention in healthy samples often apply clinical measures used to identify defects, which results in ceiling effects and

makes any enhancement induced by modafinil unobservable (Battleday & Brem, 2013).

However, there has been a more adequate response to these methodological issues in literature for executive attention compared with alerting attention. Studies including cognitively challenging tasks demonstrate that modafinil may enhance executive functioning (Battleday & Brem, 2015). In one such study, Geng et al. (2013) requested that participants guess which side of the screen an upcoming stimulus would appear in for each of 400 trials. For the first half of the task, the stimulus was more likely to occur on one side 70% of the time. For the second half it occurred equally on both sides. Geng et al. (2013) found that modafinil improved probability learning (an executive function). Furthermore, RT to the target was decreased when the target occurred where the participant predicted, indicating a corollary enhancement of spatial orienting. This is consistent with the understanding that top-down projections from the frontal and parietal lobes influence excitatory and inhibitory biases in the visual field (Hopfinger & West, 2006). These findings support the expectation for modafinil to enhance executive attention, as well as being suggestive of orienting enhancement.

The Revised Attentional Network Task

The Revised Attentional Network Task (R-ANT) (Neuhaus et al., 2010) is designed to test the alerting, orienting and executive networks of attention, as well as their interactions. Efficiency of each network is examined by changes in RT to a target resulting from particular cue types. Targets may be preceded by no cue (the continuation of the fixation point), a central cue (an asterisk appearing over the fixation point, or two asterisks presented above and below the screen) or a spatial cue (an asterisk that appears above or below the fixation point). When there is no cue, the

participant is in a state of relative readiness, as they are aware that the target will appear at some stage (tonic alertness). Central cues are more informative than no cue, acting as a warning signal and eliciting a state of phasic alertness and preparedness for the upcoming target. Alerting is indexed by the difference between RT to the target for trials with no cue compared to those with central cues. Spatial cues always validly predict the location of the subsequent target. This activates the orienting network and makes spatial cues more informative than central cues. Therefore, orienting is indexed by the difference between RT after central cues compared with spatial cues. The subsequent target is a central arrow in a horizontal row of five, which may appear above or below the fixation point. The participant's task is to decide whether the target is pointing left or right and use a button press to indicate their choice. The target stimuli are presented with flankers such as congruent or incongruent arrows. This elicits executive attention as responding to the incongruent trials requires the participant to inhibit the influence of the flanking stimuli. Executive attention effects can be calculated by comparing RT to the target after incongruent trials with congruent or neutral trials.

Neuhaus et al. (2010) found that RT decreased with cue informativity. Participants were slowest for no cue, faster for central cues and fastest for spatial cues, with differences between all types being significant. The differences in cue types is indicative of their ability to engage the alerting and orienting attentional networks. Target type elicited the executive network as expected, as RT was significantly faster to congruent compared with incongruent targets.

Electrophysiological Correlates of Attention

Event-related potentials (ERPs) are fluctuations in electrical activity in the brain that are time-locked to a stimulus or cognitive event (Luck, 1995). ERPs can be

applied to directly measure neural activity that is linked with particular attentional mechanisms (Luck, 1995). The occipital N1 ERP is a negative component which peaks maximally at around 150ms post-stimulus. It is thought to index voluntary orienting to stimuli in the sensory field, as well as the processing of this stimuli (Näätänen & Michie, 1979; Vogel & Luck, 2000). Neuhaus et al. (2010) found that the N1 ERP component was modulated by both alerting and orienting cues. They reported that target locked N1 amplitude was lowest for no cue, higher for alerting cues and highest for spatial cues. This suggests that orienting towards, and processing of, a target increases with cue informativity. If modafinil enhances alerting or orienting aspects attention, this pattern of amplitude may be expected to be greater in a modafinil condition in comparison with a placebo condition.

Rationale, Aim and Hypotheses

Previous studies investigating the effects of modafinil in healthy persons have tended to incorporate attentional measures into large cognitive batteries rather than looking at specific mechanisms of attention. It appears that the measures of attention employed have sometimes been simple and under-sensitive or confounded by other variables (Liepert & Weiller 2004; Turner, 2003; Winder-Rhodes et al., 2010). When these limitations are better addressed, studies indicate that modafinil improves sustained attention, suggesting an influence on the alerting network of attention (Baranski et al., 2004; Theunissen et al., 2009, Randall et al., 2005).

The current study aimed to address these methodological concerns by employing the ANT-R to measure specific attentional mechanisms which correspond to three separable attentional networks. Additionally, regular nicotine smokers were excluded from the study and participants were asked to consume equal levels of

caffeine on both drug and placebo sessions in a within-subjects design. Intake of both and a measure of IQ were all collected, to identify any influence of these factors.

There has been very little research which has specifically examined separate aspects of the attentional networks, particularly orienting and the phasic component of alerting. Furthermore, there has been no previous research which has investigated the ERPs underlying the attentional effects of Modafinil in a healthy sample. Thus, the present study aimed to investigate the effects of 200mg of modafinil on behavioural (RT and accuracy) and neural (N1 ERP component) measures of attentional alerting and orienting in healthy humans using an ANT-R paradigm.

Consistent with previous research, it was hypothesised that RT would be slowest for targets preceded by no cue, faster for central cues and fastest for orienting cues. The influence of modafinil on norepinephrine and sustained attention tasks suggests that modafinil enhances alerting attention (Baranski et al., 2004; de Saint Hilaire et al., 2001; Theunissen et al., 2009, Randall et al., 2005). If modafinil does enhance phasic alertness, a significantly greater reduction in RT between baseline and post-ingestion for targets preceded by central cues, for the modafinil relative to the placebo condition is expected.

No previous research has investigated the effects of modafinil on the orienting network. It was alternatively hypothesised that if modafinil directly enhances the orienting network, there would be a significantly greater reduction in RT for targets between the central and spatial cues from baseline to post-ingestion for the modafinil condition relative to the placebo condition.

Consistent with previous research, it was hypothesised that overall, N1 amplitude would be lower for targets preceded by no cue, greater (i.e., more negative) for alerting cues and greatest for orienting cues. If modafinil has a direct

effect on alerting, it was hypothesised that there would be a greater significant increase in N1 amplitude for central cues for the modafinil relative to placebo condition. If modafinil has a direct effect on orienting, it was hypothesised that there would be a greater increase in N1 amplitude between central and spatial cues for the modafinil relative to placebo condition.

Method

Participants

An a priori power calculation indicated that 20 participants were required to detect moderate sized effects (*f*=.25) with power of 0.8. The current study recruited 19 participants and the results for one were excluded from analysis, because he did not complete the second session. The final sample consisted of 18 males aged between 19-27 years old (*M*=21, *SD*=2.3). As reimbursement for time and travel costs, participants received $80. First year psychology students could receive a combined reimbursement of $40 and four hours course credit. Participants were excluded if they were regular smokers, currently using psychoactive medication, daily paracetamol/ibuprofen users, or had illicit substance use that was recent (<6 weeks) or notable (>10 lifetime uses). Participants were also excluded if they had a history of medical, neurological or mental disorders. Those who indicated potential alcohol abuse or dependence were excluded (scores $\geq$ 16 on the Alcohol Use and Disorders Identification Test [AUDIT]; Babor, Higging-Biddle, Saunders, & Monteiro, 2001). Additionally, participation was not permitted for those experiencing high levels of psychological distress (score $\geq$30 on the Kessler Psychological Scale [K10]; Andrews & Slade, 2001) or those at risk of psychosis (scores $\geq$1 on the Psychosis Screener; Degenhardt, Wall, Korten, & Jablensky, 2005 and/or scores >17 on the Schizotypal Personality Questionnaire-Brief [SPQ-B];

Raine & Benishay, 1995). To reduce the chance of adverse reactions to modafinil, participants were required to have a moderate caffeine intake (1-7 times weekly) and a body mass index >18 (unlikely to be underweight).

Materials and Apparatus

Screening questionnaires.

The Alcohol Use Disorders Identification Test (AUDIT). The AUDIT is a measure of alcohol abuse and dependence with strong validity (Babor et al., 2001; de Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009). It has eight items addressing frequency of alcohol consumption on a five-point scale and two addressing severity of the behaviour on a three-point scale. A score $\geq$ 16 indicates potential problematic alcohol use (Babor et al., 2001).

The Kessler Psychological Distress Scale (K10). The K10 is a 10-item questionnaire that offers an indication of global psychological distress (Andrews & Slade, 2001). This measure is reliable and valid for identifying the presence of a current mental disorder (Cornelius, Groothoff, van der Klink, & Brouwer, 2013). The questions are based on frequency of feelings of depression and anxiety over the past month (e.g. "how often did you feel hopeless?"). Responses are given on a scale from 1 (None of the time) to 5 (All of the time). Those who score >30 are considered to be at a high risk of psychological distress.

The Psychosis Screener. The Psychosis screener is a four-item (plus two sub-items) questionnaire used to identify people at risk of psychosis (Degenhardt et al., 2005). The questions are in regard to whether the respondent has ever experienced serious symptoms of psychosis, which they may respond to with 'Yes' or 'No'. This measure has a strong ability to identify participants experiencing symptoms at a

diagnostic level (Degenhart et al., 2005). Any 'Yes' response is considered indicative of psychosis risk.

The Schizotypal Personality Questionnaire-Brief (SPQ-B). The SPQ-B can be used to identify the presence of schizotypal personality traits with acceptable internal consistency (Raine & Benishay, 1995). It contains 22 true-false items that fall within three domains; cognitive-perceptual, disorganised and interpersonal. A point is given for each "true" response, with higher scores indicating high schizotypy. Those who score >17 are considered to be at a high risk of psychological distress.

Demographic Measures.

The Wechsler Test of Adult Reading (WTAR). The WTAR is a measure of verbal intelligence that is a strong predictor of full-scale IQ (Wechsler, 2001; Green et al., 2008). It is comprised of 50 irregularly spelled words that the participant is asked to pronounce. A point is given for each correct pronunciation, with higher scores indicating higher intelligence.

Wakefulness and Affect Measures. Wakefulness and affect measures were completed at baseline and post-ingestion of 200mg modafinil/placebo for each session, with the exception of the VAS for Subjective Drug Effects, which was only collected post-ingestion.

The Karolinska Sleepiness Scale (KSS). The KSS is a subjective measure of present fatigue. The nine-point scale ranges from 'extremely alert' to 'extremely sleepy-fighting sleep', with higher scores indicating greater fatigue.

Profile of Mood States- Short Form (POMS-SF). The POMS-SF (Shacham, 1983) was used as a subjective measure of mood. It is self-administered, requiring participants to rate their present experience of 37 adjectives on a 5-point Likert scale

(from 0=not at all to 4=extremely). This results in a Total Mood Disturbance score (ranging from 0-148), as well as scores for subscales; Tension-Anxiety (0-24), Depression- Dejection (0-32), Anger-Hostility (0-28), Vigour-Activity (0-24), Fatigue-Inertia (0-20), Confusion-Bewilderment, (0-20). Higher scores are indicative of higher mood disturbance.

Visual Analogue Scales (VAS). VAS were used as a subjective measure of perceived ability to perform attentional tasks and drug effects (Hartley, 2011). Each VAS consisted of four statements, which the participants indicated their degree of agreement with by marking a position along a 10cm horizontal line. The distance (cm) from the beginning of the line to the marked point was measured and used as the score for each statement (ranging 0-10). The two end-points indicated strongly disagree (0) and strongly agree (10) for the Subjective Performance VAS. The four Subjective Performance VAS statements included feelings of alertness, ability to perform attentional tasks, unimpaired driving ability and capacity to drive safely. The statements for the Subjective Drug Effects VAS related to strength and liking of the drug, levels of alertness and intoxication.

The Revised Attentional Network Task (ANT-R).

The ANT-R task was based on Neuhaus et al., 2010 and stimuli were presented on an 18-inch screen using NeuroScan STIM 3.1 software (see figure 1). Instructions appeared before each trial began. All instructions and stimuli were white and appeared on a black background.

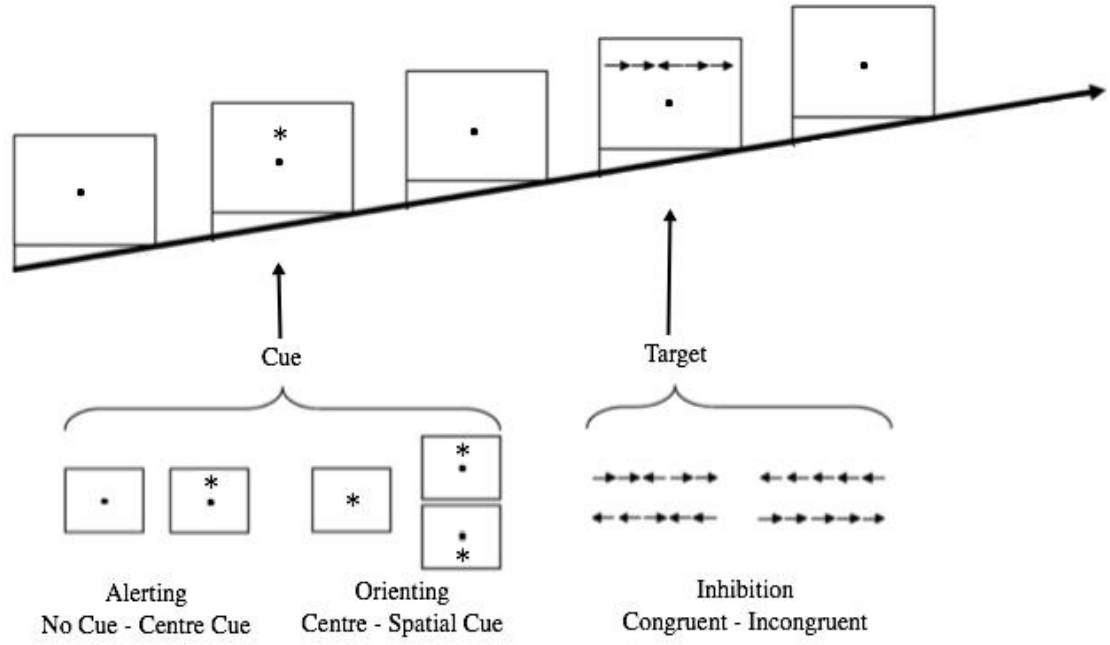


Figure 1. An illustration of the ANT-R (adapted from Neuhaus et al., 2010).

The task began with 10 practice trials in both versions. The baseline test phase consisted of 192 randomly ordered trials in a single block (9.76 minutes). The experimental test phase consisted of 576 randomly ordered trials in four blocks with breaks to minimise fatigue (39 minutes plus breaks). A fixation point (white dot) appeared in the centre of the screen throughout the task. After the instructions, one of three equiprobable cue stimuli (no cue or an asterisk, .387cm in length) appeared for 100ms. For the central, alerting cue, an asterisk was presented directly on top of the fixation point. For the spatial cue it was presented 1.01 degrees above or below the fixation point. Spatial cues always validly predicted the upcoming location of the target. After the cue stimuli, the target stimuli appeared, comprising of five arrows in a horizontal row (3.4cm long). The participant's task was to indicate the direction of the centre arrow using a left or right button press with their respective index fingers, on a NeuroScan response pad. Arrows adjacent to the central target were either

pointing in the same direction (congruent) or pointing in the opposite direction (incongruent). Responses were collected between 150-1500ms post-target.

The original task included a double cue as well as a neutral flanker option. In the current task, the central cue replaced the role of the double cue as they were both alerting cues that were not notably statistically or theoretically different (Neuhaus et al., 2010). As the executive network was not the focus of the current study, the neutral flankers were also removed to increase the number of trials. The inclusion of the congruent and incongruent flanker was sufficient to identify flanker effects. The original task also had variable inter-trial intervals that were jittered (1,200ms, 1,100ms, 1,000ms, 900ms excluding the response window) in the current study for programming ease.

Electrophysiological Recording. A NeuroSCAN system and 32-channel Quik cap were applied to record eletrophysiological activity. Continuous EEG data was recorded from 32 sites according to the 10-20 system of electrode placement. Electrodes were referenced to the mastoids and electrode impedance was kept below 10kΩ. Horizontal electro-occulographic (EOG) activity was recorded at the outer canthi of both eyes and vertical EOG was recorded above and below the left eye. Data was sampled at a rate of 1000Hz and averaged offline for a 1000ms epoch commencing 100ms prior to stimulus presentation.

The behavioural and continuous EEG data were merged together for editing. They were filtered using a Zero-phase-shift low pass filter (30Hz, 24 dB/Oct). To reduce the influence of eye blinks on the electrode channels ocular artefact reduction was conducted. Next, epoch extraction was set from -100-900ms post target stimulus onset. An automated baseline correction was applied as well as an artifact rejection, set at 70 microvolts. The occipital N1 component was derived from grand averaged

waveforms and defined as the maximum amplitude between 80-140ms from the onset of the targets. These peaks were derived using an automatic peak picking procedure and followed with visual inspection. Changes were only made if the peak fell slightly outside the allocated time window.

Procedure

The University of Tasmania Health and Medical Human Research Ethics Committee approved the project (Appendix A). Each participant voluntarily gave written informed consent (Appendix B, C, & D). After they contacted the researchers, a preliminary screening interview was conducted over the phone regarding age, smoker status, caffeine intake, BMI, drug and medical history, current medications, as well as brief versions of the AUDIT, SPQ and K10 (Appendix E). A more comprehensive screening questionnaire was self-completed at the beginning of their first experimental session (Appendix F). Eligible participants completed two four-hour sessions, at least one week apart to avoid residual effects of modafinil. To control for fatigue due to circadian rhythm all sessions were conducted between 12-5pm. Prior to each session, the researcher confirmed that the participant was being collected by someone else, rather than driving. Participants were told to have a light meal before each session, consume caffeine as usual, and abstain from paracetamol/ibuprofen and alcohol for 24-hours before and after each session. In case of any adverse reactions, the researchers were first-aid trained and reminded participants to seek a doctor, if necessary, post-experiment.

Sessions differed by capsule condition (200mg modafinil or placebo), which was counterbalanced across participants by a researcher who was absent during the experimental sessions. The study was double blind, with experimental researchers receiving the capsules in envelopes labelled with participant and session numbers.

Pre-ingestion, participants self-completed the experimental questionnaire. For session one, this included demographic information as well as the extended screening (the full SPQ, K10 and AUDIT). For both sessions, participants reported their morning caffeine and food intake and completed measures of mood (POMS-SF, see Appendix G), subjective wakefulness (the KSS and VAS, see appendix H and I), and the baseline ANT-R. After capsule ingestion, participants had a waiting period to allow for drug absorption. They read, studied, or watched television in a private room for two hours before being setup for electrophysiological recording. Previous research indicates that plasma levels peak 2-4 hours post-ingestion of modafinil (Minzenberg & Carter, 2008). Two and a half hours post-ingestion, participants began two computer tasks including the experimental ANT-R, in a counterbalanced order. Tasks took approximately 50 minutes. Participants were requested to respond to the tasks both accurately and quickly, whilst minimising their eye and body movements. Afterwards, they completed post-ingestion measures of subjective wakefulness (the KSS and VAS), mood (POMS), drug effects (VAS, see appendix J), as well as a side effects checklist (see appendix K). Finally, they offered a certainty rating from 0-100% as to whether they had consumed the active drug that session. The second session followed the same format. Finally, each participant was debriefed, thanked and received compensation for their time (monetary reimbursement and/or course credit).

Design and Data Analysis

The assumptions of ANOVA were checked to ensure the data was appropriate for this analysis. One participant was identified as a consistent outlier for most cue types in the RT analysis, but was retained in analyses as preliminary analysis showed that their results did not significantly influence the main effects and

interactions. Two separate 3x2x2x2x2 repeated measures ANOVAs were conducted to analyse the effect of Cue type (central, spatial or no cue), Drug (modafinil or placebo), Time (baseline or post consumption), and Congruency (congruent or incongruent) on reaction time (milliseconds) and accuracy (as a percentage of correct responses). For these measures, planned comparisons were conducted to assess the effect of drug over time for each cue type.

The electrophysiological dependent variable was target locked peak amplitude of the N1 ERP component. N1 amplitude was analysed at the left (O1) and right (O2) occipital electrode sites. A third repeated measures ANOVA was conducted to analyse the amplitude of the N1 ERP component with the additional variable of site (O1 or O2) and without the variable of time, as ERP data was only collected post-ingestion. For N1 amplitude, planned comparisons were conducted to assess the effect of drug by cue.

A series of paired-samples t-tests were conducted to check for differences in control variables (caffeine, sleep, fatigue, alertness, POMS-SF total and subscales) at baseline. Paired-samples t-tests were also conducted to analyse whether Subjective Drug Effects (VAS reports of strength, liking, alertness and intoxication) at post-ingestion were significantly different between drug conditions.

Four separate 2x2 repeated measures ANOVAs were conducted to analyse each of the Subjective Performance ratings (VAS reports of alertness, attention ability, unimpaired driving and driving safe) by Drug (placebo, modafinil) and Time (baseline and post-ingestion). Six separate 2x2 repeated measures ANOVAs were conducted to analyse each of the POMS-SF subscale ratings (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigour-Activity, Fatigue-Inertia and Confusion-Bewilderment) by Drug (placebo, 200mg modafinil) and Time (baseline

and post-ingestion). The main effects of Drug and Time on participants certainty (0-100%) that they had taken modafinil was analysed with a related-Samples Wilcoxon signed Rank Test.

For all dependent variables, only main effects and interactions that were hypothesis relevant or related to Drug are reported. As the variable of Cue had three levels, sphericity was not assumed and Greenhouse-Geisser corrections were applied for effects involving this variable. Partial-eta squared clarified effect sizes for omnibus ANOVAs. For tests of simple effects, Hedges *g* was applied, as it accommodates for smaller sample sizes compared with Cohen's *d*, and was interpreted as 0.2=small, 0.5=moderate, 0.8=large (Cohen, 1991).

Results

Demographic and Screening Variables

All participants were fluent English speakers who had completed year 12, with most (89.9%) enrolled in university at the time of testing. They were predominantly of average intelligence (WTAR) and fell within a healthy weight range (BMI), with some variability. None of the sample indicated problematic levels of alcohol use (AUDIT), risk of psychosis (SPQ) or psychological distress (K10) (Table 2).

Manipulation Check

A Related-Samples Wilcoxon signed Rank Test indicated that participants were significantly more certain that they had consumed modafinil in the active condition (M=48.3, SD=34.93) compared with the placebo condition (M=21.6, SD=25.5), Z=2.31 p=.021.

Table 2

Mean Age, BMI and Raw Scores for Demographic and Screening Variables

Variable	*M (SD)*	*Range*
Age (years)	21 (2.3)	8
BMI	23 (4.2)	16
Problematic Alcohol Use (AUDIT)	3.8 (3.0)	10
Risk of Psychosis (SPQ)	3.5 (4.9)	17
Psychological Distress (K10)	13.2 (4.9)	15
General Intellectual Functioning (WTAR)	35.7 (5.9)	22

Note: for more detail around these variable measures including cutoffs, see method.

Baseline Measures

At baseline, participants indicated no significant differences on several confounding variables including caffeine intake, alertness (VAS), fatigue (KSS) and mood (POMS), between drug conditions (See Table 3).

Table 3

Group Means, Standard Deviations in Parentheses, and Paired Samples T-Test Results for Control Variables at Baseline

Baseline Measure	Modafinil *M* (*SD*)	Placebo *M* (*SD*)	*t* *(1,17)*	*p*	*g*
Caffeine Intake	0.5 (0.9)	0.6 (0.8)	.809	.430	0.33
Sleep (Hours)	7.5 (1.1)	7.7 (1.2)	.732	.474	0.17
Fatigue (KSS)	4.7 (1.0)	4.7 (1.2)	.181	.859	0.04
Alertness (VAS)	3.6 (1.3)	3.7 (1.3)	.486	.633	0.08
POMS-SF (Total mood disturbance)	17.7 (10.9)	17.1 (10.5)	.485	.634	0.05
POMS-SF subscales					
Tension-Anxiety	3.0 (3.5)	2.9 (3.6)	.140	.891	0.03
Depression-Dejection	1.3 (2.1)	1.2 (2.2)	.334	.742	0.05
Anger-Hostility	0.3 (1.2)	0.3 (0.7)	-.251	.805	0.00
Vigour-activity	8.5 (5.9)	8.6 (4.6)	-.169	.868	-0.02
Fatigue-Inertia	2.8 (2.8)	1.9 (2.0)	1.699	.108	-0.36
Confusion-Bewilderment	1.8 (2.2)	2.1 (3.1)	-.531	.602	-0.11

Note: For caffeine intake means represent the number of relevant products consumed prior to the session.

Mood (POMS-SF)

There was a significant Drug x Time interaction for the Depression-Dejection, Vigour-Activity and Fatigue-Inertia subscales of the POMS-SF (see Tables 4 and 5). Planned comparisons indicated a significant decrease in Vigour-Activity and increase in Fatigue-Inertia between baseline and post-ingestion for

placebo but no significant change for modafinil. Furthermore, at post-ingestion, participants reported significantly lower Vigour-Activity after placebo, compared with modafinil, p=.002, g=1.04. There was a significant decrease in Depression-Dejection between baseline and post-ingestion for modafinil, but no significant change for placebo. For mood, all other differences between modafinil and placebo at post-ingestion were not significant, p>0.05 (See Appendix L, Table 6).

Subjective Performance and Subjective Drug Effects

There was a main effect of Time on subjective performance components relating to driving ability (see Table 7). Across drug conditions, participants were less inclined to agree that they felt able to drive unimpaired or safely at post-ingestion compared with baseline (see Table 8). There was a significant Drug x Time interaction for the Alertness and Attention Ability components of the VAS. Planned comparisons indicated a significant decrease in Subjective Alertness and Attentional Ability between baseline and post-ingestion for placebo, but not for modafinil.

At post-ingestion, participants reported significantly stronger drug effects for modafinil (M=36.3, SD=29.5) compared with placebo (M=20.4, SD=21.7), t(17)=2.15, p=0.46, g=0.60. They also reported higher liking for modafinil (M=57.5, SD=20.6) compared with placebo (M=40.5, SD=20.0), t(17)=2.79, p=.012, g=0.82

Table 4

Differences between baseline and post-ingestion fatigue and mood within each drug condition

	Modafinil				Placebo			
Measures	Baseline	Post	*p*	g	Baseline	Post	*p*	*g*
Fatigue (KSS)	4.72 (1.02)	4.22 (1.73)	.077	0.34	4.67 (1.24)	6.11 (1.41)	.608	0.26
POMS-SF subscales:								
Tension-Anxiety	3.00 (3.46)	3.72 (5.07)	.520	0.16	2.89 (3.60)	2.00 (2.95)	.252	1.06
Depression-Dejection	1.33 (2.09)	0 (0)	.015	0.88	1.22 (2.21)	1.28 (3.27)	.933	0.02
Anger-Hostility	0.28 (1.18)	0.06 (0.24)	.449	0.25	0.33 (0.69)	0.28 (0.96)	.854	0.06
Vigour-Activity	8.50 (5.92)	9.83 (6.21)	.325	0.21	8.61 (4.59)	4.44 (3.62)	<.001	0.99
Fatigue-Inertia	2.83 (2.81)	4.28 (3.37)	.184	0.46	1.94 (2.01)	6.44 (4.63)	<.001	1.23
Confusion-Bewilderment	1.78 (2.16)	1.83 (2.92)	.917	0.02	2.06 (3.08)	2.33 (3.12)	.523	0.09

Note: Post refers to Post-Ingestion

Table 5

Interactions and Main Effects of Drug and Time for Mood Measures

	Drug			Time			Drug x Time		
POMS-SF Subscales	*F*	*p*	η^2_p	*F*	*p*	η^2_p	*F*	*p*	η^2_p
Tension-Anxiety	3.49	.079	.170	0.02	.901	.001	1.45	.245	.079
Depression-Dejection	1.35	.261	.074	1.74	.205	.093	4.83	.042	.221
Anger-Hostility	1.00	.331	.056	0.30	.593	.017	0.35	.564	.020
Vigour-Activity	8.86	.008	.343	3.34	.085	.164	15.7	.001	.480
Fatigue-Inertia	1.50	.238	.081	16.6	.001	.494	4.90	.041	.224
Confusion-Bewilderment	1.69	.210	.091	0.20	.664	.011	0.14	.712	.008

Note: Degrees of freedom 1, 17 for all.

Table 7

Interactions and Main Effects of Drug and Time for Subjective Fatigue and Performance Measures

	Drug			Time			Drug x Time		
Measures	*F*	*p*	η^2_p	*F*	*p*	η^2_p	*F*	*p*	η^2_p
KSS	12.8	.002	.429	2.70	.118	.137	9.60	.007	.360
VAS Subjective Performance									
Subscales:									
Alert (1)	11.1	.004	.395	0.50	.490	.028	7.94	.012	.318
Attention Ability (2)	7.56	.014	.308	13.0	>.001	.577	8.71	.009	.339
Driving Unimpaired (3)	0.73	.404	.041	17.0	.002	.433	2.07	.169	.108
Driving Safe (4)	0.18	.679	.010	23.2	.001	.500	0.001	.981	.000

Note: Degrees of freedom 1, 17 for all.

Table 8

Subjective Performance Ratings at Baseline and Post-Ingestion by Drug

	Modafinil			Placebo		
Subjective Performance	Baseline	Post	*p*	Baseline	Post-Ingestion	*p*
Alert	3.63 (1.09)	2.89 (2.16)	.189	3.74 (1.45)	5.08 (2.11)	.034
Attention Ability	2.34 (1.26)	2.84 (2.24)	.307	2.58 (1.16)	4.84 (2.03)	<.001
Driving Unimpaired	1.47 (2.38)	2.97 (2.56)	.019	1.45 (2.12)	3.81 (3.04)	.002
Driving Safe	9.61 (1.88)	2.63 (2.86)	.003	1.12 (2.26)	2.81 (2.92)	.010

Note: Degrees of freedom 1, 17 for all.

Table 9

Percentage of Participants who Reported Side Effects by Drug Condition

Side Effects	Placebo (%)	Modafinil (%)	*p*
Headache	16.7	5.6	.625c
Nausea	11.1	0	N/A
Dry Mouth	11.1	38.9	.063
Runny Nose	5.6	0	N/A
Sore Throat	0	0	N/A
Nervousness	5.6	11.1	N/A
Dizziness	11.1	16.7	1.000c

Note: Significance = Mcnemar value.

Reaction Time

For RT descriptive statistics see Table 10. There was a large and significant main effect of Cue on RT, $F(1.55,26.39) = 250.8$, $p < .001$, $\eta^2_p = .951$. Overall, participants responded slowest to the target when no cue was provided (M=512.6, SD=35.9) faster when it was preceded by an alerting cue (M=494.6, SD=35.0) and fastest after a spatial cue (M=439.6, SD=31.4). Pairwise comparisons indicated these differences between cues were all significant (all ps <.001). Overall, participants were significantly faster when responding to congruent (M=444.72, SD=35.00)

compared with incongruent trials *(M* =519.79, *SD* = 33.99), *F* (1, 17) =279.426, *p* < .001, η^2_p=.943.

Table 10

Means for Reaction Time (ms) by Drug, Congruency, Cue and Time

			Baseline		Post-Ingestion	
Drug	Congruency	Cue	*M*	*SD*	*M*	*SD*
Modafinil	Congruent	NC	475.7	60.2	469.9	35.7
		CC	453.4	52.0	441.5	34.2
		SC	410.4	43.6	399.5	29.1
	Incongruent	NC	552.3	52.8	544.7	36.1
		CC	550.9	52.9	522.1	32.5
		SC	477.2	56.7	457.7	30.4
Placebo	Congruent	NC	473.2	45.5	487.1	48.2
		CC	445.3	48.4	457.0	46.3
		SC	415.1	42.3	408.5	41.9
	Incongruent	NC	533.8	42.5	564.0	51.5
		CC	544.7	50.8	542.2	57.8
		SC	471.8	46.7	476.1	57.3

Note: NC = No Cue; CC = Central Cue; SC = Spatial Cue

The Cue x Congruency interaction was also significant, $F(1.70, 28.85)=34.32$, $p <.001$, $\eta^2_p=0.669$. While RT decreased significantly with cue informativity for both congruent and incongruent trials, *ps*<.001, the difference between no cue and central cue conditions (alerting effect) was of moderate magnitude, $g=0.67$, for congruent trials, and of small magnitude for incongruent trials, $g=0.24$. The difference between central and spatial cues (orienting effect) was large for both congruent, $g=1.9$, and incongruent, $g=1.9$, trials.

There were non-significant main effects of Drug, $F(1,17)=.296$, $p=.594$, $\eta^2_p=.017$, and Time, $F(1,17) =0.173$, $p=.683$, $\eta^2_p=.010$. However these effects were qualified by a significant Drug x Time interaction, $F(1, 17)=4.54$, $p=.048$, $\eta^2_p=.211$. Pairwise comparisons indicated a non-significant difference between baseline compared with post-ingestion for the placebo condition, $p=.151$, $g=0.19$, and a small but non-significant decrease for the modafinil condition $p=.280$, $g=0.34$. At baseline, there was a non-significant difference between the modafinil and placebo, $p=.658$, $g=0.12$, conditions. However, at post-ingestion, there was a moderate magnitude effect which approached significance, with lower RT for modafinil compared with placebo, $p=.064$, $g=0.41$.

The hypothesised Drug x Time x Cue interaction was non-significant, $F(1.63, 27.72)=2.418$, $p=.116$, but had a moderate effect size, $\eta^2_p=.125$ (see Figure 1). Planned pairwise comparisons were conducted to assess the effect of Drug over Time for each Cue type. When the target was preceded by no cue, between baseline and post-ingestion there was a small, significant increase in RT for placebo, $p=.011$, $g=0.48$, but no significant change for modafinil, $p=.536$, $g=0.14$. Furthermore, at post-ingestion, RT was shorter for modafinil compared with placebo ($M=525.58$, $SD=11.27$), $p=.030$, $g=0.71$.

When the target was preceded by a central cue, there was a small, significant decrease in RT between baseline and post-ingestion for modafinil, p=.040, g=0.33, but no significant change for placebo, p=.541, g=0.09. For central cue trials, there was a trend towards faster RT at post-ingestion for modafinil compared to placebo, p=.071, and this was a small effect, g=0.43.When the target was preceded by a spatial cue, there was a small but non-significant decrease in RT between baseline and post-ingestion for modafinil (p=.136, g=0.37), but no significant change for placebo (p=.892, g=0.03). For spatial cue trials, there was a small but non-significant decrease in participants RT at post-ingestion for modafinil, compared with placebo, p=.158, g=0.34).

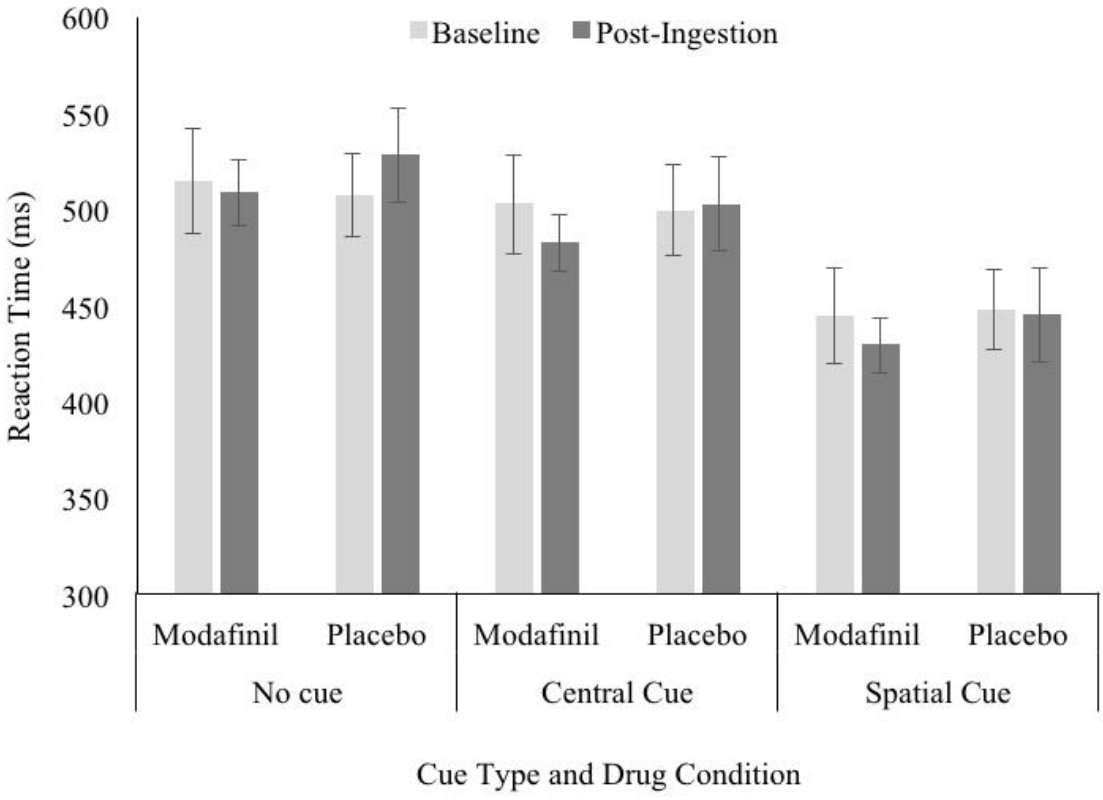


Figure 1. Reaction Time at Baseline and Post-Ingestion by Cue and Drug (error bars indicate 95%CIs)

There was also a significant Drug x Time x Congruency interaction, $F(1,17)=3.088$, $p=.002$, $\eta^2_p=.435$ (see Figure 2 and Figure 3). Further analysis indicated a significant Drug x Time interaction for incongruent trials, $F(1,17)=6.732$, $p=.019$, $\eta^2_p=.284$, but not for congruent trials, $F(1,17)=2.415$, $p=.139$, $\eta^2_p=.124$. For incongruent trials in the modafinil condition, there was a small-moderate decrease in RT at post-ingestion compared with baseline that was trending towards significance, $p=.096$, $g=0.43$. However, for incongruent trials in the placebo condition, there was a small non-significant difference in reaction time at baseline compared with post-ingestion, $p=.265$, $g=0.21$.

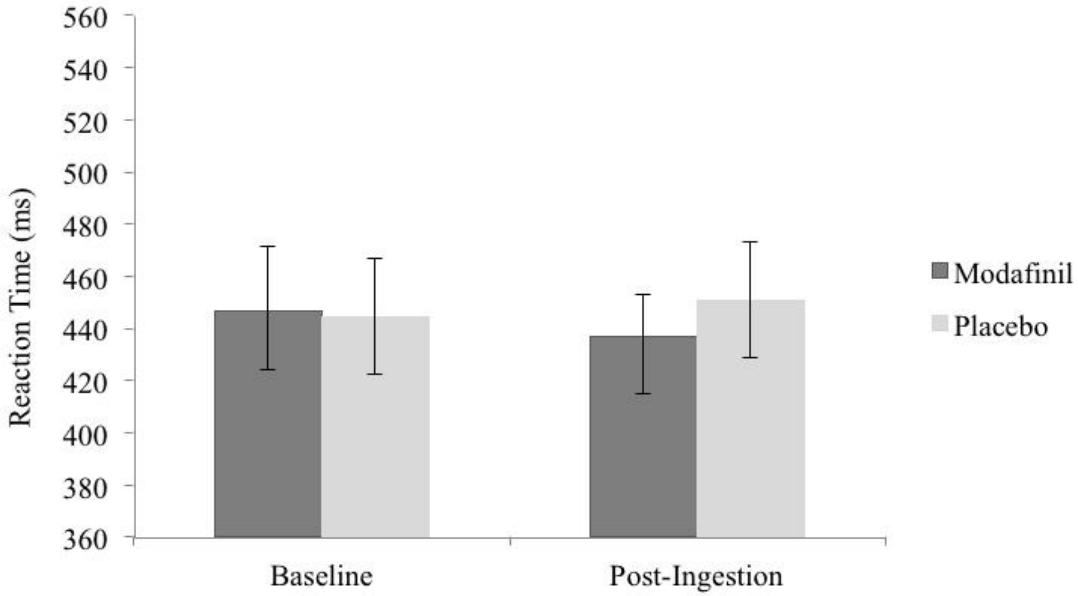
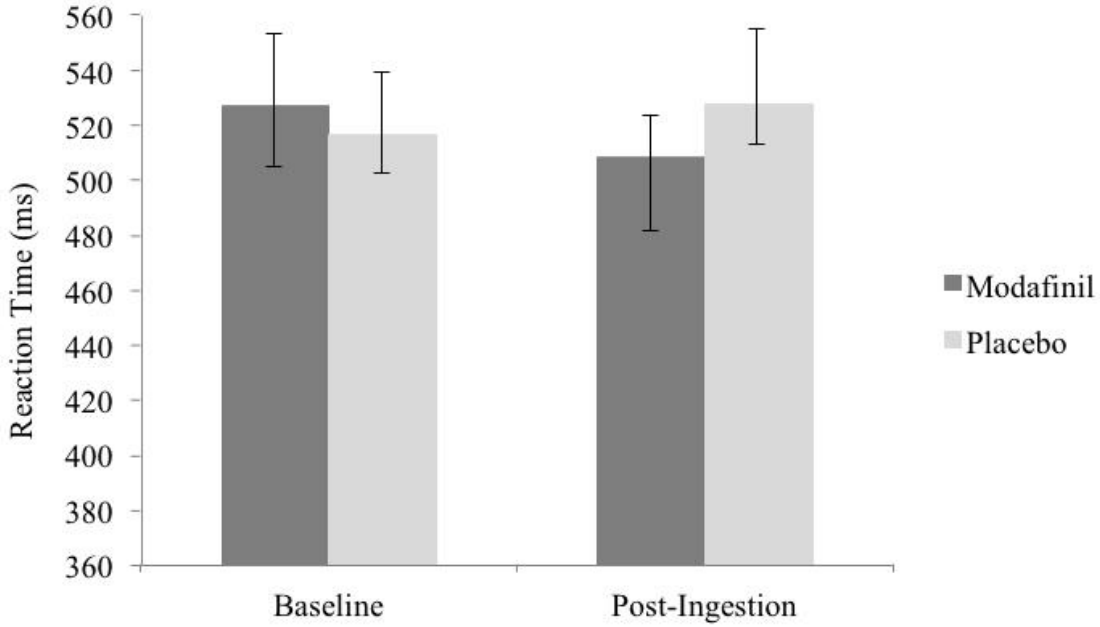


Figure 2. Mean Reaction Time (ms) for targets following congruent cues at baseline and post-ingestion for the modafinil and placebo conditions (error bars represent 95% CIs).

Furthermore, for incongruent trials, there was a small decrease in RT for modafinil compared with placebo at post-ingestion that was trending towards significance, $p=.061$, $g=0.43$. For incongruent trials, there was a small, but non-significant difference between modafinil and placebo RT at baseline $p=.497$, $g=0.20$.

Figure 3. Mean Reaction Time (ms) for targets following incongruent cues at



baseline and post-ingestion for the modafinil and placebo conditions (error bars represent 95% CIs).

Accuracy

For accuracy, descriptive statistics are shown in Table 11. The main effects of Cue, $F(1.73,29.40)=18.92$, $p<.001$, $\eta 2p=.527$, Congruency, $F(1,17)=52.21$, $p<.001$, $\eta 2p=.754$, and the interaction between the two, $F(1.88,31.9)=12.09$, $p<.001$, $\eta 2p=.416$, were all significant.

For congruent trials, accuracy was significantly higher after spatial cues compared with no cue, $p=.013$, $g=0.34$, and central cues, $p=.001$, $g=0.24$. For congruent trials, accuracy was not significantly different for trials preceded by no cue compared with central cues, $p=.202$, $g=0.13$.

Table 11

Means for Accuracy (as a percentage) by Drug, Congruency, Cue and Time

			Baseline		Post-Ingestion	
Drug	Congruency	Cue	*M*	*SD*	*M*	*SD*
Modafinil	Congruent	NC	94.5	15.8	97.1	4.2
		CC	94.6	15.5	97.9	3.1
		SC	95.4	15.6	98.3	2.6
	Incongruent	NC	90.9	15.1	93.6	4.5
		CC	89.4	16.1	91.0	6.9
		SC	93.1	15.7	96.2	2.8
Placebo	Congruent	NC	98.1	2.4	96.2	3.9
		CC	97.9	4.6	96.3	3.4
		SC	97.1	4.6	97.2	3.6
	Incongruent	NC	93.9	6.3	90.9	6.1
		CC	94.4	4.4	88.8	6.0
		SC	96.7	3.5	94.3	5.3

Note: NC = No Cue; CC = Central Cue; SC = Spatial Cue

For incongruent trials, accuracy was moderately and significantly higher after spatial cues, compared with no cue p=.001, g=0.77, and central cues, p<.001, g=1.18.

For incongruent trials, accuracy was moderately and significantly, higher for trials preceded by no cue compared with central cues, p=.004, g=0.48. For accuracy, there were no other significant main effects or interactions (ps>.05, see Appendix M, Table 12).

Peak N1 Amplitude

Figure 4 shows grand mean averaged ERP waveforms for target locked trials for each of the three cue-type conditions. See Table 13 for the descriptive statistics for N1 amplitude to the target.

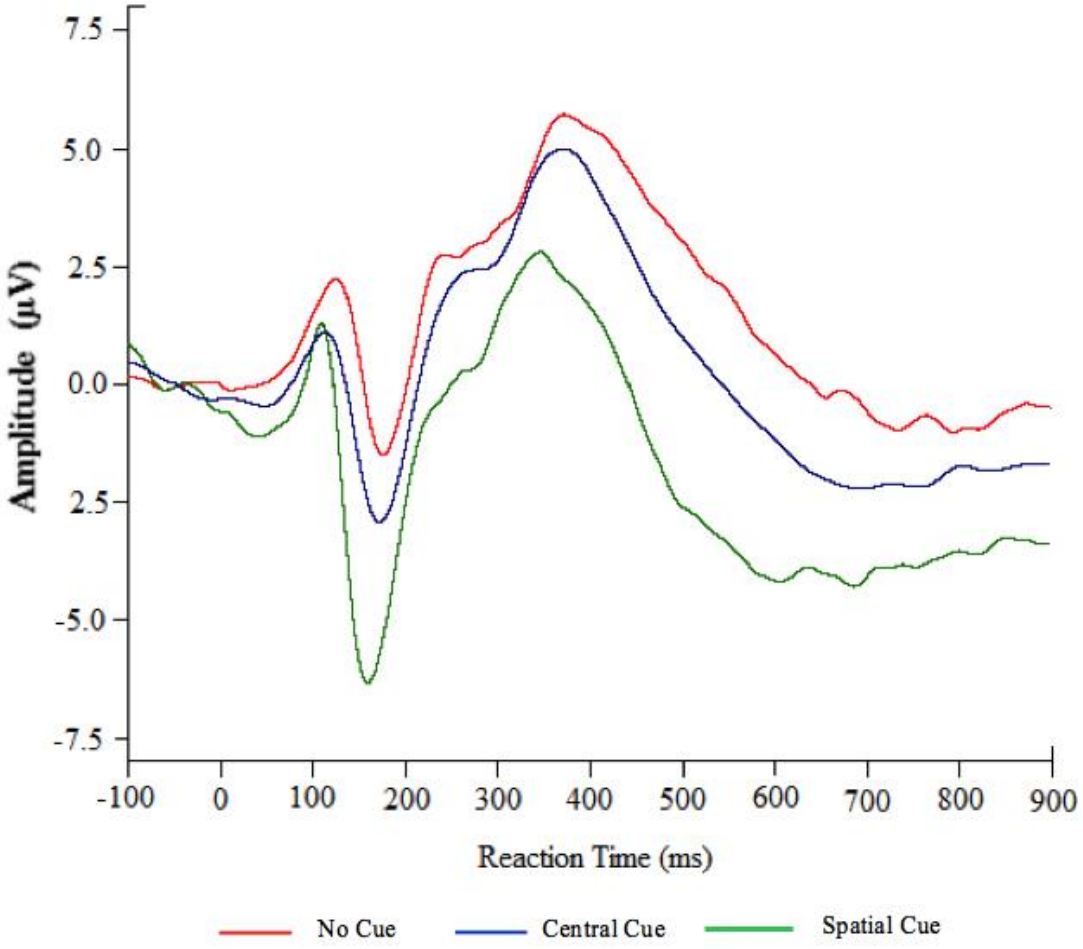


Figure 4. Grand Means for Target Locked N1 ERP Amplitude for Congruent Trials by Cue Type.

Table 13

Mean Peak N1 Amplitude to Targets by Site, Congruency and Cue

			Modafinil		Placebo	
Site	Congruency	Cue	Mean	SD	Mean	SD
01	Congruent	NC	-2.48	3.37	-1.95	2.86
		CC	-4.65	3.79	-4.06	3.56
		SC	-7.55	3.63	-6.94	4.12
	Incongruent	NC	-2.71	3.51	-1.98	3.06
		CC	-4.46	4.10	-3.64	3.75
		SC	-7.51	4.14	-6.85	3.56
02	Congruent	NC	-1.96	2.03	-1.49	2.04
		CC	-4.36	2.44	-3.49	2.34
		SC	-6.50	2.96	-6.04	3.40
	Incongruent	NC	-2.01	2.24	-1.69	2.20
		CC	-3.91	2.91	-3.27	2.88
		SC	-6.61	3.18	-5.79	2.72

Note: NC = No Cue; CC = Central Cue; SC = Spatial Cue.

There was a significant main effect of cue on N1 amplitude, $F(1.5,25.8)=64.25$, $p<.001$, $\eta 2p=.793$. There was a large, significant increase in target locked N1 amplitude for spatial cues (M=-6.7 SD=2.9) compared with central

cues (*M*=-3.9, *SD*=3.0), *p*<.001, *g*=0.87, and no cues (*M*=-2.0, *SD*=2.5), *p*<.001, *g*=1.85. There was also a moderate, significant increase in N1 amplitude for central cues compared with no cue (*g*=0.69). The main effect of drug approached significance, with greater N1 amplitude for the modafinil condition (*M*=-4.6, *SD*=2.8) compared with placebo (*M*=-3.9, *SD*=2.7), *F*(1,17)=3.06, *p*=.098, *g*=0.25.

The hypothesised Drug x Cue interaction was non-significant, *F*(1.6,27.7)=0.14, *p*=.833, η2p=.008 (see Figure 5). Planned comparisons were conducted to analyse any differences in N1 amplitude by cue type. They revealed that when preceded by central cues, there was a small, significant enlargement of target locked N1 amplitude for the modafinil compared with the placebo condition, *p*=.046, *g*=0.23. Similarly, when the target was preceded by no cue, the average N1 amplitude was greater in the modafinil condition, compared with placebo. However, this effect was small and only trending towards significance, F(1,17)=3.61, *p*=.075, *g*=0.20. When the target was preceded by a spatial cue there was no significant difference in N1 amplitude between the modafinil condition, and the placebo condition, *F*(1,17)=1.09, *p*=.311, *g*=0.19.

The Drug x Cue x Congruency x Site interaction was trending towards significance, *F*(1.7, 29.4)=2.61, *p*=.093, η2p=.133, but was not of interest to the current study. All other main effects and interactions were non significant (See Appendix N, Table 14).

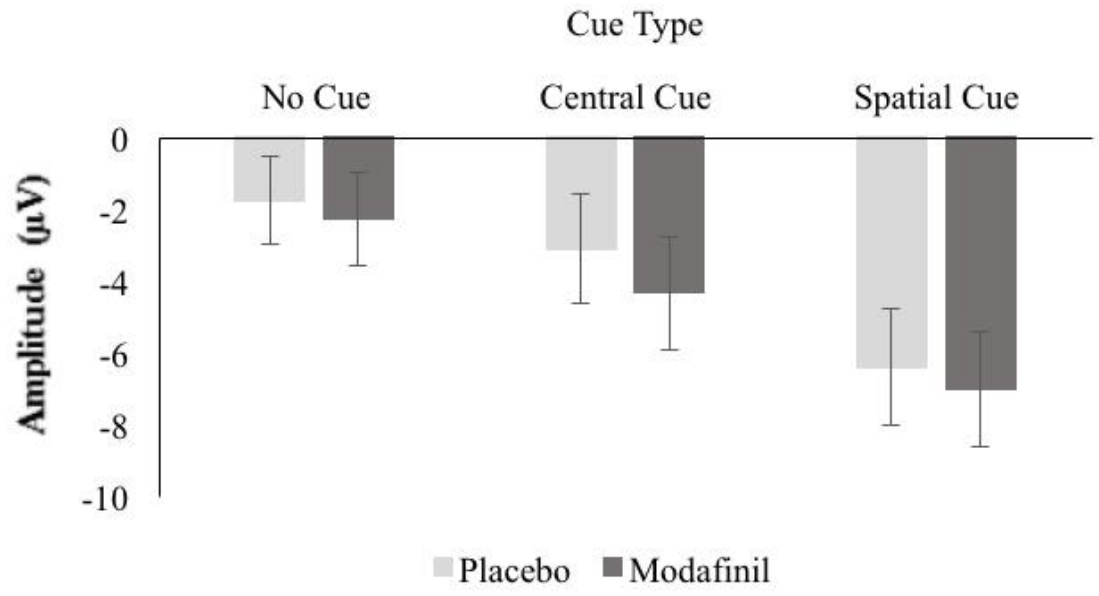


Figure 5. N1 amplitude by Drug and Cue

Discussion

The present study investigated the effects of 200mg of modafinil on behavioural (reaction time and accuracy) and neural (N1 ERP component) measures of attentional alerting and orienting in healthy humans using an ANT-R paradigm. As hypothesised, RT decreased and N1 amplitude increased with cue informativity, across drug conditions. The results supported the hypotheses that if modafinil enhanced the alerting network, there would be a significantly greater reduction in RT and a significant increase in N1 amplitude following central cues, for the modafinil relative to the placebo condition. Furthermore, there was an unexpected enhancement of RT and N1 for no cue trials, for the modafinil relative to the placebo condition. These results indicate that modafinil may enhance the tonic and phasic components of the alerting network. There was an equivalent enhancement of the orienting network that was not greater than the alerting effects. The self-report data indicates that these effects of modafinil may have been the result of reduced feelings of fatigue experienced at post-ingestion. The accuracy analysis indicated no significant

differences between the drug conditions, thus differences for RT between drug conditions cannot be accounted for by a speed-accuracy trade-off.

The blinding procedure appears to have been successful. Within both conditions, participants tended to report low certainty (on a 0-100% rating) that they had consumed modafinil. They were significantly more certain in the active condition than for the placebo condition, but participants' capacity to guess the correct condition was lower than chance (50%). Side effects did not differ significantly between conditions.

Reaction Time

As hypothesised, RT decreased with cue informativity; participants were slowest for no cue, faster for central cues and fastest for spatial cues Additionally, RT was slower for congruent relative to incongruent trials. The orienting effect was of similar magnitude for both congruencies, whilst the alerting effect was larger for congruent compared with incongruent trials. These effects indicate that the task elicited differences that were consistent with theorised attentional networks (Neuhaus et al., 2010).

The results for the modafinil condition indicated a small, significant decrease in RT from baseline to post-ingestion for central cues (g=0.33) and a small, non-significant decrease for spatial cues (p=.136, g=0.37). These findings may indicate enhancement of the alerting network for the modafinil condition relative to placebo, as expected. The results for the spatial cues indicate an enhancement of orienting between baseline and post-ingestion for modafinil in comparison with placebo. However, this effect was not significant, nor greater in magnitude than the central cue effect. This negates the alternative hypothesis that if modafinil directly enhances the orienting network, there would be a significantly greater reduction in RT for

targets between the central and spatial cues from baseline to post-ingestion for the modafinil condition relative to the placebo condition.

The significant increase in RT for no cue trials at post-ingestion compared with baseline for placebo, but not modafinil, was not hypothesised. It may suggest that modafinil alleviated fatigue induced by the sustained nature of the task, enhancing tonic alertness. This is consistent with previous findings that modafinil enhances performance on sustained attention tasks, a marker of tonic alertness (Baranski et al., 2004; Theunissen et al., 2009, Randall et al., 2005). Baranski et al. (2004) observed enhanced sustained attention, demonstrated by improved accuracy on the DRN and faster RT on the SRT, when participants ingested modafinil compared with placebo. Similarly, Theunissen et al. (2009) found a large, significant reduction in RT for the MC task when participants consumed modafinil compared with placebo, indicating enhanced sustained attention. Randall et al. (2005) found that participants who received modafinil were faster on the RVIP compared to placebo controls. The findings of the current study are consistent with these observations that modafinil enhances tonic alertness. The results are inconsistent with previous studies that have reported no effect of modafinil on sustained attention (Liepert et al., 2004, Winder-Rhodes et al., 2010). These studies used simple attention tasks, likely eliciting ceiling effects as they were not cognitively challenging. In contrast, the current study incorporated incongruent flankers, increasing cognitive load and better allowing any enhancing effect of modafinil to be observable. Furthermore, the current sample was larger and more likely to experience enhancement as they had no nicotine dependence.

The significant, small, g=0.33, decrease in RT between baseline and post – ingestion for central cues in the modafinil condition suggests a further enhancement

for phasic alertness that is distinct to the enhancement of tonic alertness. Only one previous study has looked specifically at phasic alertness, and they found no enhancing effect of modafinil compared with placebo for no cue trials, *g*=0.14, or alerting cue trials, *g*=0.08 (Liepert et al., 2004). The current findings are likely more reliable due to the larger sample and more challenging task, which may have made the study comparably more sensitive to detecting small effects.

Reduced RT to no cue trials indicates that modafinil may enhance tonic alertness, which may partially underlie the enhancement of phasic alertness. However, this effect was comparatively smaller and less significant than the effect observed for no cue trials. This is preliminary evidence that modafinil targets and enhances the tonic and phasic components of alerting attention. This seems to produce reduced RT to spatial cue trials (orienting) that is equivalent to the effects observed earlier and arguably the result of the interdependence of the attentional networks, as opposed to being a targeted effect of the drug.

While not the main focus of the present thesis, there was a significant Drug x Time x Congruency interaction for RT, such that Drug x Time interaction was significant for incongruent trials but not congruent trials. For incongruent trials in the modafinil condition, there was a small-moderate decrease in RT at baseline compared with post-ingestion that was trending towards significance (*p*=.096, *g*=0.43), and this tended to be lower in comparison to placebo at baseline (*p*=.061, *g*=0.43). However, for placebo, there was a small non-significant difference in RT at baseline compared with post-ingestion, (*p*=.265, *g*=0.21). Thus it is possible that Modafinil increased participant's capacity to inhibit the incongruent flankers, suggesting that modafinil enhances executive attention. Although unhypothesised, this is consistent with findings of enhanced executive functions for modafinil

compared with placebo, and the understanding that modafinil increases dopamine, a neurotransmitter that supports these functions (Geng et al., 2013). The original ANT-R included a neutral target; a central arrow flanked with straight lines that were neither congruent nor incongruent. In the current study, neutral targets were omitted to maximise trials for each cue type, as executive attention was not the focus. Future research could better investigate these effects of modafinil on executive attention by incorporating neutral targets and comparing responses between neutral and incongruent trials to isolate the inhibitory control component of the task.

N1 Component

As hypothesised, N1 amplitude increased with cue informativity. This is consistent with previous findings for this task and indicates that it elicited the attentional networks as expected (Neuhaus, 2010). The drug x cue interaction was non-significant. Further analysis revealed a small, significant increase in N1 amplitude for targets preceded by central cues for the modafinil condition compared with placebo. This is indicative of enhancement of phasic alertness, and consistent with the hypothesis that if modafinil has a direct effect on alerting there would be a greater significant increase in N1 amplitude for central cues for the modafinil relative to placebo condition.

The results indicated no significant increase in N1 amplitude for spatial cues. This suggests that modafinil does not directly enhance the orienting component of attention. For no cue trials, there was an unexpected trend towards a significant increase in N1 amplitude for modafinil compared with placebo. This is potentially indicative of modafinil increasing tonic alertness which may have caused some of the increase in phasic alertness for modafinil compared with placebo. However, the magnitude of the enhancement was greater for central cues than for no cue and

spatial cues. This suggests that modafinil consumption may directly enhance tonic and phasic alertness.

There is no previous research investigating the ERP correlates of attention relative to modafinil consumption. The N1 ERP component is known to index orienting towards and processing of stimuli (Näätänen & Michie, 1979; Vogel & Luck, 2000). The current results indicate modafinil may enhance this function as a consequence of improved functioning of both the tonic and phasic components of the alerting network, with some consequential enhancement of the orienting network. This is consistent with the behavioural results, which also indicated a potential increase in tonic and phasic alerting, as observed by decreased RT for no cue and central cue trials for modafinil compared with placebo. Furthermore, a similar enhancement of the orienting network was observed, demonstrated by an equivalent reduction in RT for spatial cue trials for modafinil but not placebo. The self-reports indicate that modafinil may have enhanced these areas of attention by alleviating the onset of fatigue and sleepiness experienced in the placebo condition.

Modafinil and Mood

Sleepiness (KSS) and Fatigue-Inertia (POMS-SF) increased between baseline and post-ingestion for placebo but not modafinil. Vigour-Activity decreased between baseline and post-ingestion for placebo, but not modafinil. Participants also reported feeling significantly less alert and capable of performing attentional tasks at post-ingestion compared with baseline for placebo but not modafinil. These findings are consistent with the reputation modafinil has as a eugoroic and previous studies that have found modafinil improves performance on sustained attention tasks (Minzenberg & Carter, 2008)(Baranski et al., 2004; Theunissen et al., 2009, Randall et al., 2005).

Self-reported feelings of Depression-Dejection were low for both drug conditions, decreasing significantly between baseline and post-ingestion for modafinil but not placebo. This is consistent with the understanding that modafinil inhibits the re-uptake of dopamine, which promotes feelings of euphoria, and has seen modafinil trialled as an anti-depressant (Malhi et al., 2016; Regenthal, Koch, Kohler, Preiss, & Krugel, 2009). Unexpectedly, for both conditions, participants felt more capable of driving well at baseline compared with post-ingestion. Participants' had been told not to drive home and indicating they were capable of doing so may have been perceived as defiant social behaviour, perhaps biasing their responses.

Practical Implications

The results of the current study suggest that modafinil may be effective for cognitive neuro-enhancement in healthy non-sleep deprived persons performing tasks that require high levels of tonic and phasic alertness, as well as executive attention. Despite the modafinil related enhancement of attention being small in magnitude and sometimes non-significant, for both RT and N1, it may be practically meaningful. This study also indicates that some orienting enhancement is observed after modafinil consumption, a small effect that can be attributed to the interdependent nature of the networks. As most off label-users tend to engage in tasks that are sustained, such as an air force officer watching a radar screen, the consumption of modafinil is likely to result in positive improvement in comparison with no drug. However, future research ought to compare the effects of modafinil with more well recognised cognitive neuro-enhancers such as caffeine, glucose and exercise (Benton, Owens & Parker, 1994; Brunyé, Mahoney, Lieberman, & Taylor, 2010; McMorris & Hale, 2012). It may be more practical for modafinil users to employ these enhancers if they are no less efficacious. Future research could also

investigate whether enhancement is still observed in shorter tasks of phasic alerting, when fatigue is minimal. Furthermore, this study is only suggestive of small enhancing effects after a single dose of 200mg of modafinil. Future research also ought to investigate the effects of modafinil on specific networks of attention at differential and repeated dosages.

Methodological Limitations

Only males aged 18-30 were recruited, which limits the generalisability of the current findings to females and other ages. A male sample was chosen based on sex differences in the N1 component. In females completing the ANT-R, a significant frontal-occipital second peak of N1 has been observed that does not occur for males (Neuhaus et al., 2009). Sex differences have also been observed in cognitive processing and these may vary based on menstrual cycles (Brotzner, Klimesch, & Kerschbaum, 2015). Furthermore, the clearance rate for modafinil is faster for young compared with older males, and is faster again for young females (Wong et al., 1999). This is suggestive of differential metabolic rates related to age and sex, indicating that performance enhancement may occur differentially for females and older populations. Future research should evaluate the efficacy of modafinil for neuro-enhancement in these groups.

The current study was limited as peak plasma levels were estimated based on past studies rather than by collecting blood samples. Therefore, the time of testing may not have been ideal for each participant due to differences in absorption. Estimating peak plasma levels was less invasive for participants, however, future research with lighter ethical constraints could address this issue.

The within-subjects design employed by the current study was both a strength and limitation. This design enabled participants to act as their own control for many

potential confounding variables (metabolic rate, stimulant tolerance, caffeine usage). As participants engaged with the task repeatedly, some degree of practice effects were suspected. Consequentially, baseline measures were taken to reduce their influence. Additionally, a preliminary mixed model analysis suggested that whilst practice effects had occurred, they did not supersede the effects of drug condition. This approach was chosen rather than incorporating order into the analysis as a between subjects variable because the study was already slightly underpowered due to sample size. As some practice effects were observed, future research may wish to carefully consider the susceptibility of their task to practice effects and choose a design accordingly.

Baseline measures were not collected for comparison with post-ingestion data for N1 amplitude. The time cost associated with EEG setup for a brief baseline task was unfeasible for the current study. If future research has the scope, they may integrate baseline measures of ERP components. Such studies should also investigate other ERP components related to attentional enhancement due to modafinil consumption. The N200, which indexes the executive function of inhibitory control, would be of particular interest, as the behavioural results provided preliminary evidence of enhancement.

Another limitation of the current study is that no eye tracking measurement was applied to check that the participants were focusing on the stimuli in the visual field as expected (Anderson, Nemrodov, Preston, & Itier, 2013). Participants were verbally instructed to focus on the fixation dot throughout the task and appeared to do so, given that the overall task effects for RT and N1 were consistent with previous research. However, future studies should utilise eye tracking to minimise type two errors (Anderson et al., 2013).

Summary and Conclusions

The present study investigated the effects of 200mg of modafinil on behavioural (reaction time and accuracy) and neural (N1 ERP component) measures of attentional alerting and orienting in healthy humans using an ANT-R paradigm. The results indicated that regardless of drug condition, RT decreased and N1 amplitude became greater with cue informativity, as hypothesised. This is tentative evidence that the task elicited the attentional networks (Neuhaus et al., 2010).

For the modafinil condition, there was a small, significant, decrease in RT from baseline to post-ingestion for central cues that suggests alerting enhancement. The reduction in RT for spatial cues indicated an enhancement of orienting, likely a consequence of the alerting effect. The increase in RT for no cue trials for placebo but not modafinil further indicates that modafinil may have prevented reductions in tonic alertness. Given that the RT reduction was greater for central compared with no cue trials, it is likely that modafinil enhances phasic alertness.

The N1 amplitude data further supported these arguments. Greater N1 amplitude occurred for central cue trials for modafinil compared with placebo, suggesting the drug enhanced alertness. As amplitude was greater for no cue trials for modafinil compared with placebo, some of the alerting effect can be attributed to increased tonic alertness, but the magnitude was greater for central than no cue conditions compared, so modafinil also appears to directly enhance phasic alertness. The increase in N1 amplitude for spatial cues was not of a greater magnitude than that observed for central cues, indicating modafinil did not enhance orienting beyond the increase of alerting attention.

The results of the current study are consistent with previous findings of tonic alerting enhancement for modafinil. However, the phasic alerting and orienting

effects are preliminary and novel, particularly for N1 amplitude. Further research is necessary to substantiate them. The finding that modafinil enhances executive alerting was not the focus of the current study and warrants investigation analysing the acute effects of modafinil on ERPs relevant to this network, such as N2. Any future studies also ought to address the limitations of the current study by investigating whether the findings can be generalised to females and other age groups with a design that improves on power by collecting blood plasma levels, eye tracking data, a greater sample size and collection of ERP data at baseline.

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List of Appendices

Appendix A: Ethics approval

Sent via email

From: Lauren.Black@utas.edu.au [mailto:Lauren.Black@utas.edu.au]
Sent: Wednesday, 30 March 2016 1:22 PM
To: Raimondo Bruno
Cc: chris.wake@dhhs.tas.gov.au; Allison Matthews; Jessica Hartley; Lauren Black
Subject: Notification of Amendment Approval: H0011386 The effect of modafinil on simulated driving performanc

Dear AssocProf Bruno

Ethics Ref: H0011386
Title: The effect of modafinil on simulated driving performance

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Health and Medical Human Research Ethics Committee on 24/3/2016:

Measurement of brain activity (EEG) during the experimental tasks Changes to the experimental tasks Omission of the baseline testing condition Registered nurse is no longer on site MODAFINIL info and consent forms_revised2016

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards

Lauren Black

--
Lauren Black
Executive Officer - Ethics
Office of Research Services
University of Tasmania
Private Bag 01
Hobart TAS 7001
Phone: (03) 6226 2764
Fax: (03) 6226 2765
Email: Lauren.Black@utas.edu.au
Web: http://www.research.utas.edu.au/

Appendix B: Information sheet

INFORMATION SHEET

The Effect of Modafinil on Cognitive Processes and Brain Activity

Chief Investigators: Dr Raimondo Bruno & Dr Allison Matthews

Researchers: Caitlin Harris & Oliver De Angelis *

**This research is being conducted as part of an Honours degree in the School of Psychology, UTAS.*

We would like to invite you to participate in a study aiming to better understand the way that the prescription drug Modafinil effects cognitive processes such as attention and associated brain activity. The use of this drug is increasing Australia wide, and we are interested in better understanding its effects. There have been a number of studies which have shown some effects of stimulant drugs on cognitive processes but very few studies have examined Modafinil. Getting a better understanding about Modafinil is particularly important, not just to understand how the drug affects cognition, but also to be able to provide information for doctors to give to potential users of the drug.

Why have I been invited to participate in this research?

You are invited to take part in the study if you are male and aged 18-30 years old. In order for the results of the study to be clear, all participants need to speak English fluently, and have had no previous neurological or mental health problems. In addition, participants must NOT use illicit drugs, smoke cigarettes daily, consume alcohol at harmful levels or be female.

What will my participation involve?

Participating in this study is unlikely to cause any discomfort or distress. Firstly, if you are interested in taking part in the study, you will be invited to complete a series of confidential screening questionnaires. These will enquire about what your mood has been like recently. This will include a psychological distress scale, schizotypal personality questionnaire, a psychosis screener and some questions regarding your alcohol, caffeine and drug use. All data collected will be kept in the strictest confidence, and the way we maintain this is described below. This screening process is simply to ensure that participants in the study are not taking medications or experiencing other issues that may cause a negative response to Modafinil.

During the study, we will ask for some basic information about yourself (such as age, sex, years of schooling). During each testing session, you will be fitted with an electrode

cap for measuring your brain activity. You will be asked to complete some computer-based tasks which relate to cognitive processes such as attention. In these tasks you will respond with a button press when particular stimuli appear on the screen. Previous studies using the same dose of Modafinil have found side effects for some participants, including dry mouth, mild headaches and mild nausea. There will be two testing sessions which will occur at the University of Tasmania, and will take around four hours each. You will be reimbursed up to $80 for your time and out-of-pocket expenses.

Before taking part in the study you must organise for a reliable friend or family member to collect you from the lab at the end of the testing session, in case you are still experiencing any effects following the possible administration of Modafinil. The researcher will check that this has been organised before the testing session begins. When the nominated person collects you, they will be given a copy of the medication information sheet about Modafinil, and the main points will be verbally explained. Namely, it will be explained that they should ensure you do not drive a vehicle or operate machinery for the rest of the day, and do not consume alcohol. In the unlikely event that you do experience unpleasant side effects while completing the testing, the researchers are trained in first aid, and the chief investigators will be available on site to provide further assistance if required. Additionally, the researcher will explain that in the unlikely event of you experiencing an adverse reaction once you have left the premises, you should contact your doctor or be taken to hospital immediately.

There are no specific risks associated with the measurement of brain activity. However, if you have sensitive skin there is a small possibility of a slight skin reaction from electrode preparation materials. If you believe there is a chance that your skin may react you are advised to reconsider participation.

How private is the information that I give?

It is important for you to know that all data collected will be kept in the strictest confidence. All data will be identified by a coding system and no names or contact numbers will appear on any records. In this way, your identity is protected, and there will be no risk of legal or social problems arising from your participating in the study. All information gathered in the study will be reported as grouped data, and because no personal information is recorded, no individual participants will be identifiable in the research output. Data from the study will be stored securely for five years in locked cabinets in the School of Psychology, as is legally required, and then destroyed by shredding.

Can I withdraw from the research if I wish?

Participation in this study is entirely voluntary. You may, at any time, decline to answer any question you so wish, or withdraw from the study without effect or explanation.

You will be given a copy of this information sheet to keep. Please retain this information sheet in case you decide at a later data that you would like to retract your data from the study.

Who do I need to contact if I have any questions about the research?

If you would like more information about the research, please contact Dr Allison Matthews on 62267236 (or email Allison.Matthews@utas.edu.au) or Dr Raimondo Bruno 6226 2190 (Raimondo.Bruno@utas.edu.au). If you would like to find out about the results of the study, these will be available from Dr Matthews after November 2016.

Has this research been approved by an ethics committee?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H0011386.

Who can I contact if I have any concerns?

If you have any personal concerns related to the study, you may choose to discuss these concerns confidentially with a counsellor at the University Psychology Clinic free of charge. Confidential appointments may be made on (03) 6226 2805.

Thank you for your interest in the study and for taking the time to read this information sheet. We hope you will be interested in participating in this study.

Raimondo Bruno & Allison Matthews

Chief Investigators

(03) 6226 2190 or (03) 6226 7236

Oliver De Angelis/Caitlin Harris

Student Researchers

Appendix C: Consent form

CONSENT FORM

The Effect of Modafinil on Cognitive Processes and Brain Activity

---

1. I have read and understood the 'Information Sheet' for this study.
2. I have read and understood the 'Consumer Medicine Information' regarding modafinil.
2. The nature and possible effects of the study have been explained to me.
3. I understand that the study involves:
    - Attending two testing sessions of approximately four hours duration
    - Completing a series of cognitive tasks while my brain activity is measured
5. I understand that all research data will be securely stored on the University of Tasmania premises for five years, and will then be destroyed.
6. Any questions that I have asked have been answered to my satisfaction.
7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
8. I understand that the researchers will maintain my identity confidential and that any information I supply to the researcher(s) will be used only for the purposes of the research.
9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so wish, may request that any data I have supplied to date be withdrawn from the research.
10. This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H0011386.

Name of Participant:

Signature: Date:

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation

Name of investigator _____

Signature of investigator Date

Appendix D: Modafinil consumer medical information

MODAVIGIL®

Modafinil

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about MODAVIGIL® tablets. As this leaflet does not contain all the available information, it is important that you talk to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you receiving MODAVIGIL® against the benefits this medicine is expected to have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet. You may need to read it again.

What MODAVIGIL® is used for

MODAVIGIL® is used to improve wakefulness in people with excessive daytime sleepiness associated with the medical condition known as narcolepsy or with Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS), or shift work sleep disorder (SWSD).

In narcolepsy, there is a sudden and irresistible tendency to fall asleep during normal waking hours. This happens at unpredictable times, even when it is inappropriate or may be unsafe to do so. MODAVIGIL® decreases this unwanted excessive daytime sleepiness.

With OSAHS, daytime sleepiness may occur due to an interrupted night time sleep. MODAVIGIL® only treats the symptom of sleepiness and does not treat the cause of OSAHS. Whilst taking MODAVIGIL® you should continue with treatments intended to help manage your underlying medical condition, such as Continuous Positive Airway Pressure, unless your doctor tells you otherwise.

MODAVIGIL® may also help to keep you awake during your working shift if you have been diagnosed with moderate to severe chronic Shift Work Sleep Disorder (SWSD).

Precisely how MODAVIGIL® works is not known, but it is known that it acts on the central nervous system (the brain). It differs from other stimulant medicines that promote wakefulness. MODAVIGIL® increases wakefulness. Unlike other stimulants it does not overstimulate or produce a "high" feeling.

Your doctor may have prescribed MODAVIGIL® for another reason. Ask you doctor if you have any questions about why MODAVIGIL® has been prescribed for you.

Before you take MODAVIGIL®

When you must not take it

You must not take MODAVIGIL® if you:

- are allergic to modafinil or any of the other ingredients listed at the end of this leaflet. (See "MODAVIGIL® tablets description"). Signs of allergic reaction may include a skin rash, itching, shortness of breath or swelling of the face, lips or tongue
- are pregnant, or likely to become pregnant.

Do not take MODAVIGIL® if the packaging is torn or shows signs of tampering or the tablets do not look quite right.

Do not take MODAVIGIL® if the expiry date on the pack has passed.

If you are not sure about whether you should start taking MODAVIGIL®, you should contact your doctor.

Before you take it

Before you start taking MODAVIGIL® you should discuss with your doctor any of the following points which apply to you. If you:

- are under 18 or over 65 years old
- have a history of mental health problems
- have heart problems, including, for example, angina (chest pain), previous heart attack, enlarged heart
- have an abnormal/irregular heart rhythm
- have high blood pressure or your high blood pressure is controlled by medication

- have kidney or liver problems
- are taking hormonal contraceptives
- could become pregnant
- are currently receiving treatment for anxiety
- are breastfeeding
- are taking brain stimulants, such as methylphenidate
- are taking any medicines to treat depression, including those called monoamine oxidase inhibitors (MAOIs)
- are taking medicines to treat epilepsy or fits, such as phenytoin, carbamazepine and phenobarbitone
- are taking medicines to treat fungal infections, such as ketoconazole and itraconazole
- are taking medicines to help you sleep (sedatives)
- are taking rifampicin, an antibiotic used to treat tuberculosis
- are taking cyclosporin, a medicine used to stop organ transplant rejection
- are taking propranolol, a medicine used to treat, for example, high blood pressure, heart problems or migraine
- are taking warfarin, a medicine used to prevent unwanted blood clotting
- are taking theophylline, a medicine used in asthma and lung problems
- are taking any other medicines, including any available without a prescription from your pharmacy, supermarket or health food shop

Tell your doctor about any of the above before you take MODAVIGIL®. Your doctor will discuss the risks and benefits of using MODAVIGIL®.

How to take MODAVIGIL®

It is important that you take this medicine as directed by the doctor. Your doctor will tell you how much you should take, when and how often. Follow your doctor's instructions. If you are unsure ask your doctor or pharmacist.

How much should you take

Each MODAVIGIL® tablet contains 100mg of modafinil.

The usual daily dose of modafinil depends on individual response. For sleepiness associated with narcolepsy or OSAHS, the dose ranges from 200mg to 400mg.

Each day you should take either:

- two MODAVIGIL® tablets

  or

- up to four MODAVIGIL® tablets.

For SWSD, a dose of 200mg is recommended.

Do not exceed the recommended daily dose unless directed to do so by your doctor.

When and how should you take the tablets

For sleepiness associated with narcolepsy or OSAHS, you should take your MODAVIGIL® tablets either:

- as two separate doses, one in the morning and one at midday,

  or

- as one dose, in the morning.

For narcolepsy or OSAHS, do not take your MODAVIGIL® tablets later than midday, or you may have trouble sleeping at night.

For SWSD, you should take your MODAVIGIL® tablets as a single dose 1 hour prior to commencing your shift work.

Swallow the tablets whole with a little water.

NOTE: Your doctor may start your treatment with less than two tablets a day.

If you need more than two tablets per day, your doctor should increase the dose stepwise, one additional tablet at a time, depending on how you respond to the treatment. The highest dose is four tablets per day.

If you are currently on another treatment for narcolepsy, your doctor will advise you how best to withdraw from that treatment and begin taking MODAVIGIL®. Other stimulants used for narcolepsy may cause a "high" feeling. Be aware therefore that you may feel different as you withdraw from other stimulants. MODAVIGIL® is not associated with this "high" feeling. It works on excessive daytime sleepiness.

MODAVIGIL® only treats the symptom of sleepiness. Other treatments intended to help manage your underlying medical condition

should still be used regularly, unless your doctor tells you otherwise. You should commence or continue disease-modifying interventions (for example, Continuous Positive Airway Pressure).

REMEMBER: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to anyone else. It may harm them, even if their symptoms appear to be the same as yours.

If you forget to take it

If you miss a dose of MODAVIGIL® tablets, just take the next dose at your usual time. Do not take an extra dose to "catch up".

While you are taking MODAVIGIL®

Things you must do

If you become pregnant while you are taking MODAVIGIL®, stop taking it and tell your doctor immediately.

If you are about to be started on any new medicine, tell your doctor and pharmacist that you are taking MODAVIGIL®.

Tell your doctor if you believe that MODAVIGIL® is not helping your condition. Your doctor may need to change the dose.

Things you must not do

Do not give MODAVIGIL® to anyone else, even if they have the same symptoms as you.

Things to be careful of

MODAVIGIL® may reduce the effectiveness of oral contraceptives. If you are using these forms of contraceptives while taking MODAVIGIL® (and for 1 month after you stop treatment with MODAVIGIL®) you should either use: an alternative birth control method or another effective birth control method together with your current contraceptive.

Do not drive or operate machinery until you know how MODAVIGIL® affects you.

Side Effects

MODAVIGIL® may cause you to have a serious rash.

Stop MODAVIGIL® and call your doctor right away or get emergency treatment if you have a skin rash, hives, sores in your mouth, or your skin blisters and peels, or if you have any sudden wheeziness, difficulty in breathing, swelling, rash or itching (especially affecting the whole body).

MODAVIGIL® may cause the following side effects in some people. In clinical studies, these side effects also occurred in people who received non-active (sugar) tablets. Tell your doctor if you notice any of these:

- headache
- nausea
- diarrhoea
- dry mouth
- poor appetite
- runny nose
- sore throat
- nervous feeling
- dizziness.

Tell your doctor immediately if any of the following occur:

- mental (psychiatric) symptoms. Symptoms include depression, anxiety, hallucinations, mania, thoughts of suicide or other mental problems.

Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything that makes you feel unwell. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Overdosage

Immediately telephone your doctor, or the Poisons Information Centre (telephone 13 11 26 in Australia or 0800 764 766 in New Zealand), or go to the emergency department of your nearest hospital, if you think you or anyone else may have taken too much MODAVIGIL®. Do this, even if there are no signs of discomfort or poisoning.

MODAVIGIL® tablets description

Each MODAVIGIL® tablet contains 100mg of modafinil.

Each tablet also contains the following inactive ingredients:

- lactose
- starch-maize
- magnesium silicate dihydrate
- sodium croscarmellose
- povidone
- purified talc
- magnesium stearate.

MODAVIGIL® tablets are white, round-shaped with smooth convex sides.

Each pack contains either 10, 30 or 60 tablets.

Storage

Keep MODAVIGIL® tablets in the original pack until it is time to take them.

Store MODAVIGIL® tablets below 25 degrees C. Keep the pack in a cool, dry place and away from direct heat and sunlight.

Do not store MODAVIGIL® tablets in the bathroom or near a sink.

Keep MODAVIGIL® tablets where children cannot reach them. A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

The Australian Registration Number is AUST R 82350.

This is not all the information available on MODAVIGIL®. If you have any more questions or are unsure about anything, ask your doctor or pharmacist.

MODAVIGIL® is supplied in Australia by:
CSL Biotherapies
45 Poplar Road
Parkville 3052 VIC
AUSTRALIA

and in New Zealand by:
CSL Biotherapies (NZ) Limited
666 Great South Road
Central Park,
Auckland 6
NEW ZEALAND
Telephone: 09 579 8105

and manufactured by:
Cephalon France
20 rue Charles Martigny
94700 Maisons-Alfort
FRANCE

This leaflet was prepared in February 2009.

MODAVIGIL® is a registered trademark owned by Cephalon, Inc.

Published by MIMS/myDr July 2009

Appendix E: Screening questionnaire

Screening questionnaire

How old are you?	_____

Participants must be males between 18 and 25.

Do you smoke nicotine? How many days a week?_____ *If regular smoker, participant is not eligible for the study.*	Yes ☐	No ☐
Is English your first language?	Yes ☐	No ☐

Have you ever used any of the following:		
Heroin	Yes ☐	No ☐
Methamphetamine (speed powder, base, ice)	Yes ☐	No ☐
Ecstasy	Yes ☐	No ☐
Cocaine	Yes ☐	No ☐
Hallucinogens (e.g. LSD, acid, magic mushrooms)	Yes ☐	No ☐
Inhalants (e.g. amyl nitrate, rush, glue, laughing gas, petrol, paint)	Yes ☐	No ☐
Other illicit drugs (cannabis)	Yes ☐	No ☐
Have you ever used pharmaceutical medications without them being prescribed to you, e.g. morphine, methadone, oxycodone, pharmaceutical stimulants, antipsychotics, antidepressants?	Yes ☐	No ☐
How recently have you used any of the above?	_____	
At your peak, how often did you use any of the above?	_____	

*If participant demonstrates **recent and/or history of regular use** (i.e. more than once a month, and within the last two years) they are **not** eligible for the study. The other potential criteria are none in the last six months and less than 10 lifetime occasions.*

Q1. How often do you have a drink containing alcohol?

0	Never	**1**	Monthly or less	**2**	2-4 times a month	**3**	2-3 times a week	**4**	4 or more times a week
Q2.	**How many drinks containing alcohol do you have on a typical day when you are drinking?**								
0	1 or 2	**1**	3 or 4	**2**	5 or 6	**3**	7 to 9	**4**	10 or more
Q3.	**How often do you have six or more drinks on one occasion?**								
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily

Do you have a history of any of the following:		
Major Anxiety/Depression	Yes ☐	No ☐
Mania	Yes ☐	No ☐
Psychosis/ any other psychological illness	Yes ☐	No ☐
Attention deficit/hyperactivity disorder	Yes ☐	No ☐
Alcohol or substance use problems	Yes ☐	No ☐
Hypertension	Yes ☐	No ☐
Cardiac problems (inc. chest pain/angina)	Yes ☐	No ☐
Liver impairment	Yes ☐	No ☐
Kidney impairment	Yes ☐	No ☐
Epilepsy	Yes ☐	No ☐
Chronic Pain	Yes ☐	No ☐
Asthma	Yes ☐	No ☐
Skin complaints	Yes ☐	No ☐
Severe head injury	Yes ☐	No ☐
Fits/convulsions	Yes ☐	No ☐
Loss of consciousness >2 minutes	Yes ☐	No ☐
Multiple concussions (or any concussion in last 6 weeks)	Yes ☐	No ☐
Regular giddiness	Yes ☐	No ☐
Sleep disorders or major sleeping difficulties	Yes ☐	No ☐

*If **yes** to any of the above, the participant is **not** eligible for the study.*

Are you currently taking any medications: (including over-the-counter medications)	Yes ☐	No ☐
For safety, please verify specifically:		
Methylphenidate (a drug used for ADHD & narcolepsy)	Yes ☐	No ☐
Triazolam (or any benzodiazepine used, for example, in the treatment of insomnia or anxiety)	Yes ☐	No ☐
Psychiatric meds for depression (inc. Herbal- hypericum St Johns Wort), or schizophrenia	Yes ☐	No ☐
Phenytoin or other anticonvulsants (any drugs used for epilepsy)	Yes ☐	No ☐
Warfarin (anticoagulant, blood thinner)	Yes ☐	No ☐
Codeine, fentanyl (or any drugs used for chronic pain)	Yes ☐	No ☐
Hormone supplements (testosterone)	Yes ☐	No ☐
Daily paracetamol or ibuprophen	Yes ☐	No ☐
Medications to treat fungal infections	Yes ☐	No ☐
Medications to help you sleep	Yes ☐	No ☐
Any other medicines, including any available without a prescription from a pharmacy, supermarket or health food store	Yes ☐	No ☐
Any medications over the past week (other than PRN paracetamol)	Yes ☐	No ☐

*if **yes** to any of the above, the participant is **not** eligible for the study.*

Caffeine use

Q1.	**How often do you have a drink containing caffiene?**				
0	Never	**1** Monthly or less	**2** 2-4 times a month	**3** 2-3 times a week	**4** 4 or more times a week
Q2.	**How many drinks containing caffiene do you have on a typical day when you have caffiene?**				
0 1 or 2		**1** 3 or 4	**2** 5 or 6	**3** 7 to 9	**4** 10 or more
Q3.	**How often do you have six or more drinks on one occasion?**				

Do you have notice any adverse side effects when you drink caffeine? Yes / No

Weight_____ kg

Height_____ cm

Estimated BMI: _____

Are you left or right handed (please circle)? Left Right

Psychosis Screener

1. In the past 12 months, have you felt that your thoughts were being directly interfered with or controlled by another person?	Yes ☐ No ☐
1a. Did it come about in a way that any people would find hard to believe, for instance, through telepathy?	Yes ☐ No ☐
2. In the past 12 months, have you had a feeling that people were too interested in you?	Yes ☐ No ☐
2a. In the past 12 months, have you had a feeling that things were arranged so as to have a special meaning for you, or even that harm might come to you?	Yes ☐ No ☐
3. Do you have any special powers that most people lack?	Yes ☐ No ☐
3a. Do you belong to a group of people who also have these special powers?	Yes ☐ No ☐
4. Has a doctor ever told you that you may have schizophrenia?	Yes ☐ No ☐

Total=

(≥1)

Note to researchers:

- **Book sessions from 1-5pm**
- **Remind participants to abstain from paracetamol/ibuprofen on the day of testing, and alcohol for 24hrs prior to testing**
- **Stick to normal caffeine routine on day of testing**
- **Have a light lunch and try to eat similar-sized meal across two sessions**

Appendix F: Experimental questionnaire and extended screening

Date ___/___/___ Participant ID _____

1. What grade of school did you complete (up to year 12/secondary school)?

Year_____

2. Have you completed any courses after school?

No……0

Yes, trade/technical……1

Yes, university……2

Specify qualifications_____

3. Are you currently studying?

No……0

Yes, trade/technical…….1

Yes, university…….. 2

Specify _____

4. How are you currently employed? Mark ONE response

Not employed ……1

Full time ……2

Part time/casual ……3

Full time student ……4

Home duties ……5

Work and study …… 6

Part-time student ……8

Other ……9

Specify_____

Experimental session questionnaire

Date ____/____/____ Participant ID _____

1. **Check that participant has abstained from alcohol for 24 hours and illicit drug use since completing the screening questionnaire**
2. **Weight _____ kg**

   Height_____ cm

   BMI _____

3. **Have you consumed any medications in the past week (or any prescribed medications since completing the screening questionnaire)?**

   If yes, please detail:

Medication	Number of occasions	Time since last used	Estimated dose

3. **How many cups of coffee (or any other caffeinated drinks/products) have you consumed today? _____**

   If > 0. How many hours since your last caffeinated drink _____ hours

4. **Have you had any tobacco or nicotine products today? Yes / No**

   If yes, how many cigarettes (or nicotine products) have you had today? ____

   If yes, How many hours since your last cigarette (nicotine product) _____ hours

5. **What have you had to eat today? How long since you last ate something?___mins**

_____

_____

_____

_____

6. **Approximately how many hours sleep did you have last night? ____**

AUDIT

These questions are related to your use of alcohol. Remember, any information you provide is completely confidential.

Please circle the most appropriate response

Q1.	**How often do you have a drink containing alcohol?**						
0	Never	**1**	Monthly or less	**2**	2-4 times a month	**3**	2-3 times a week	**4**	4 or more times a week
Q2.	**How many drinks containing alcohol do you have on a typical day when you are drinking?**						
0	1 or 2	**1**	3 or 4	**2**	5 or 6	**3**	7 to 9	**4**	10 or more
Q3.	**How often do you have six or more drinks on one occasion?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q4.	**How often during the last year have you found that you were not able to stop drinking once you had started?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q5.	**How often during the last year have you failed to do what was normally expected from you because of drinking?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q6.	**How often during the last year have you needed a first drink in the morning to get yourself going, after a heavy drinking session?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q7.	**How often during the last year have you had a feeling of guilt or remorse after drinking?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q8.	**How often during the last year have you been unable to remember what happened the night before because you had been drinking?**						
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q9.	**Have you or someone else been injured as a result of your drinking?**						
0	No	**2**	Yes, but not in last year			**4**	Yes, during the last year		
Q10.	**Has a relative or friend or doctor or other health worker been concerned about your drinking or suggested you cut down?**						
0	No	**2**	Yes , but not in last year			**4**	Yes, during the last year		

Total= (>19)

These questions are related to how you have been feeling over the last 4 weeks. Remember, any information you provide is completely confidential.

Please circle the most appropriate response.
In the last 4 weeks, about how often –

1. Did you feel tired out for no good reason?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

2. Did you feel nervous?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Note: If response 1 chosen, go to Q4

3. Did you feel so nervous that nothing could calm you down?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

4. Did you feel hopeless?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

5. Did you feel restless or fidgety?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Note: If response 1 chosen, go to Q7

6. Did you feel so restless that you could not sit still?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

7. Did you feel depressed?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

8. Did you feel that everything was an effort?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

9. Did you feel so sad that nothing could cheer you up?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

10. Did you feel worthless?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Total=

(≥30)

SPQ

Please answer each item by checking Y (Yes) or N (No). Answer ***all*** items even if unsure of your answer. When you have finished, check over each one to make sure you have answered them.

1. People sometimes find me aloof and distant	Yes ☐	No ☐
2. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes ☐	No ☐
3. People sometimes comment on my unusual mannerisms and habits	Yes ☐	No ☐
4. Are you sometimes sure that other people can tell what you are thinking?	Yes ☐	No ☐
5. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes ☐	No ☐
6. Some people think that I am a very bizarre person	Yes ☐	No ☐
7. I feel I have to be on my guard with friends	Yes ☐	No ☐
8. Some people find me a bit vague and elusive during a conversation	Yes ☐	No ☐
9. Do you often pick up hidden threats or put downs from what people say or do?	Yes ☐	No ☐
10. When shopping do you get the feeling that other people are taking notice of you?	Yes ☐	No ☐
11. I feel very uncomfortable in social situations involving unfamiliar people	Yes ☐	No ☐
12. Have you had experiences with astrology, seeing the future, UFos, ESP, or a sixth sense?	Yes ☐	No ☐
13. I sometimes use words in unusual ways	Yes ☐	No ☐
14. Have you found that it is best not to let other people know too much about you?	Yes ☐	No ☐
15. I tend to keep in the background on social occasions	Yes ☐	No ☐
16. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	Yes ☐	No ☐
17. Do you often have to keep an eye out to stop people from taking advantage of you?	Yes ☐	No ☐
18. Do you feel that you are unable to get 'close' to people?	Yes ☐	No ☐
19. I am an odd, unusual person	Yes ☐	No ☐
20. I find it hard to communicate clearly what I want to say to people	Yes ☐	No ☐
21. I feel very uneasy talking to people I do not know well	Yes ☐	No ☐
22. I tend to keep my feeling to myself	Yes ☐	No ☐

Total=(≥17)

Participant Code:

Test Point:

PROFILE OF MOOD STATES-SHORT FORM

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer to the right, which best describes how you are feeling AT THE MOMENT.

The numbers refer to these phrases:
0=not at all
1=a little
2=moderately
3=quite a bit
4= extremely

1. Tense.....0 1 2 3 4
2. Angry.....0 1 2 3 4
3. Worn out.....0 1 2 3 4
4. Unhappy.....0 1 2 3 4
5. Lively.....0 1 2 3 4
6. Confused.....0 1 2 3 4
7. Peeved.....0 1 2 3 4
8. Sad.....0 1 2 3 4
9. Active.....0 1 2 3 4
10. On Edge.....0 1 2 3 4
11. Grouchy.....0 1 2 3 4
12. Blue.....0 1 2 3 4
13. Energetic..... 0 1 2 3 4
14. Hopeless.....0 1 2 3 4
15. Uneasy.....0 1 2 3 4
16. Restless.....0 1 2 3 4
17. Unable to Concentrate.....0 1 2 3 4
18. Fatigued.....0 1 2 3 4
19. Annoyed.....0 1 2 3 4
20. Discouraged.....0 1 2 3 4
21. Resentful.....0 1 2 3 4
22. Nervous.....0 1 2 3 4
23. Miserable.....0 1 2 3 4
24. Cheerful.....0 1 2 3 4
25. Bitter.....0 1 2 3 4
26. Exhausted.....0 1 2 3 4
27. Anxious.....0 1 2 3 4
28. Helpless.....0 1 2 3 4
29. Weary.....0 1 2 3 4
30. Bewildered.....0 1 2 3 4
31. Furious.....0 1 2 3 4
32. Full of pep.....0 1 2 3 4
33. Worthless.....0 1 2 3 4
34. Forgetful.....0 1 2 3 4
35. Vigorous.....0 1 2 3 4
36. Uncertain about things.....0 1 2 3 4
37. Bushed.....0 1 2 3 4

Appendix H: Karolinska Sleepiness Scale

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Appendix I: Visual analogue scale subjective performance

Participant number: **Test point:**

Visual Analogue Scales of Subjective Performance

Please mark on each line at the point which most accurately reflects your level of agreeness AT THE MOMENT with the below statement:

1. I feel alert

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

2. I feel that I will be able to perform the attentional tasks to the best of my ability

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

3.I do not feel that my driving would be impaired right now

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

4.I feel capable of driving safely right now

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

Appendix J: Visual analogue scale drug effects

Participant number: Test point:

Visual Analogue Scales of Subjective Drug Effects

Please mark on each line at the point which most accurately reflects your level of agreeness AT THE MOMENT with the below statement:

1. Strength of drug effect

NO EFFECT ——————————————————————— VERY STRONG EFFECT

2. Liking of the drug effect

DISLIKE VERY MUCH ——————————————————————— LIKE VERY MUCH

3. Alert level

NOT ALERT ——————————————————————— VERY ALERT

4. Intoxication

NOT INTOXICATED ——————————————————————— VERY INTOXICATED

From 0-100%, how certain are you that you received modafinil today?

_____

Appendix K: Side effects checklist

During this experimental session have you experienced any of the following symptoms?

Yes	No	
☐	☐	headache
☐	☐	nausea
☐	☐	dry mouth
☐	☐	runny nose
☐	☐	sore throat
☐	☐	nervous feeling
☐	☐	dizziness

Are you currently experiencing any other adverse symptoms? Please specify.

_____

Appendix L

Table 6

Group Means for Fatigue and Mood by Drug Condition at Post-Ingestion

	Modafinil	Placebo	*p*	*g*
POMS-SF subscales				
Tension-Anxiety	3.72 (5.07)	2.00 (2.95)	.062	0.41
Depression-Dejection	0 (0)	1.28 (3.27)	.116	-0.54
Anger-Hostility	0.06 (0.24)	0.28 (0.96)	.215	-0.31
Vigour-Activity	9.83 (6.21)	4.44 (3.62)	.002	1.04
Fatigue-Inertia	4.28 (3.37)	6.44 (4.63)	.067	-0.52
Confusion-Bewilderment	1.83 (2.92)	2.33 (3.12)	.095	-0.16

Note…

Appendix M

Table 12

Main Effects and Interactions for Accuracy

Factor	*F*	*df*	*p*	η2p
Time	0.01	1, 17	.937	.000
Drug	0.25	1, 17	.624	.014
Cue	18.92	1.7, 29.4	.001	.527
Congruency	52.21	1, 17	.001	.754
Time x Drug	1.71	1, 17	.208	.091
Time x Cue	2.54	1.71, 29.06	.103	.130
Time x Congruency	11.69	1, 17	.003	.407
Drug x Cue	0.43	1.9, 31.6	.641	.025
Drug x Congruency	0.00	1, 17	.982	<.001
Cue x Congruency	12.09	1.9, 31.9	<.001	.416
Time x Drug x Cue	1.64	1.5, 26.0	.215	.088
Time x Drug x Congruency	2.17	1, 17	.159	.113
Time x Cue x Congruency	1.46	27.3, 319.1	.249	.079
Drug x Cue x Congruency	0.92	1.9, 33.0	.410	.051
Time x Drug x Cue x Congruency	0.15	1.7, 29.4	.834	.009

Appendix N

Table 14

Main Effects and Interactions of Site, Drug, Cue and Congruency for Peak N1 Amplitude

Factor/s	*F*	*df*	*p*	η2p
Site	2.75	1, 17	.115	.139
Drug	3.06	1, 17	.098	.153
Cue	64.25	1.5, 25.7	<.001	.791
Congruency	0.44	1, 17	.516	.025
Drug x Site	0.04	1, 17	.844	.002
Cue x Site	2.26	1.4, 23.5	.139	.117
Congruency x Site	0.03	1, 17	.876	.001
Drug x Cue	0.14	1.6, 27.7	.833	.008
Drug x Congruency	0.13	1, 17	.728	.007
Cue x Congruency	1.69	1.7, 29.3	.205	.090
Drug x Cue x Site	0.80	1.9, 31.8	.450	.045
Drug x Congruency x Site	1.06	1, 17	.318	.059
Cue x Congruency x Site	0.03	1.6, 27.3	.947	.002
Drug x Cue x Congruency	0.07	1.9, 33.0	.932	.004
Drug x Cue x Congruency x Site	2.61	1.7, 29.4	.093	.133